# THE YEAR BOOK *of* MEDICINE

(1958 1959 YEAR BOOK *Series*)

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Dentistry

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PAUL B BEESON MD

# PART I

# INFECTIONS

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## ANTIBIOTICS—GENERAL

**Severe Reactions to Antibiotics** Nation Wide Survey conducted by Henry Welch C N Lewis H I Weinstein and B B Boeckman[1] included 800 hospital —about a third of the hospital beds available in general hospitals in the United States—and interviews with 1 600 physicians As each of the 16 districts of the Food and Drug Administration supplied trained investigators to obtain all case reports and pertinent data the number of cases undetected in the areas investigated was probably small None of the reactions reported in this survey has previously been recorded in medical journals All severe reactions were sought including blood dyscrasia exfoliative dermatiti severe angioneurotic edema severe monilial or fungal infections and enterocolitis

From late 1953 to early 1957 3 419 severe reactions occurred in the areas studied Of the e 1 925 were excluded because they were not severe enough to be life threatening Of the 1 070 severe reactions 809 were of the anaphylactoid type and of these 793 resulted from penicillin The second largest group of life threatening reactions (107) were the superinfections Of 74 cases of staphylococcic enterocolitis 44 followed abdominal surgery In this series 26 patients died and 18 of these had had abdominal surgery Of the 70 with severe skin reaction 7 (10%) died

Of 611 anaphylactoid reactions following intramuscular injection 63 were fatal One nonfatal reaction followed intravenous injection of procaine penicillin and streptomycin intravenous injection of an insoluble salt of penicillin is a highly questionable procedure Of 122 anaphylactoid shocks that followed intramuscular injection of penicillin with streptomycin or dihydrostreptomycin 9 were fatal Thus of the 733 reactions following intramuscular injection of peni

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(1) A t l ot & Ch moth 4 800 813 D mb 19 7

cillin or penicillin with streptomycin or dihydrostreptomycin 72 (about 10%) were fatal Of 49 reactions of the anaphylactoid type following oral administration of penicillin preparations none was fatal

Of 46 cases of severe blood dyscrasias reported and classified 27 (over 50%) were fatal Chloramphenicol was associated with 12 cases of aplastic anemia (9 fatal) 3 of granulocytopenia (1 fatal) and 1 fatal case of thrombocytopenic purpura There were 16 cases of anaphylactoid or hemorrhagic purpura

In 1956 about 2 500 000 lb of antibiotics were produced in this country Penicillin accounted for 960 000 lb or 38% of the total Until 1945 only one type of penicillin was available now there are 121 preparations commercially available Over the years penicillin has been injected fed spread insufflated and sprayed intra abdominally intra cisternally intrapleurally and intravaginally No surface or cavity has remained inviolate Penicillin has saved tens of thousands of lives in the past 14 years and the tremendous reduction in mortality morbidity and complicating diseases has affected the lives of millions Nevertheless major advances in drug therapy inevitably are accompanied by untoward side actions varying from mild transient skin reactions to acute shock and death

Penicillin is the antibiotic causing the greatest number of reactions and is most often involved in fatal cases The oral route is safest from the standpoint of both number of reactions and mortality Three anaphylactoid shocks followed tetracycline therapy and 1 chloramphenicol Allergic reactions to these drugs are extremely rare and no previous anaphylactoid reactions have been reported Most reactions occurred after administration of the antibiotic under supervision of a physician

► [This points up the fact that penicillin despite its remarkable freedom from direct toxicity is responsible for a considerable number of serious allergic reactions —Ed ]

**Problems of Antibiotics in Food as Food and Drug Administration Sees Them** are reviewed by Henry Welch[7] Penicillin has become a billion dollar industry with over 440 tons produced last year and 150 preparations available for clinical use today It has a potential for sensitizing cer

(7) Am J P b Heal h 47 01 05 Ju 195

tain unfortunate persons whether prescribed or inadvertently through eating or drinking foods containing it

Of 1706 milk samples from cows treated for mastitis by intramammary infusion tested in 48 states 5 9% contained penicillin Opinions of 30 authorities in the field of antibiotic therapy indicated that such concentrations were unlikely to modify the oral or intestinal flora cause emergence of resistant strains or provoke sensitization of an insensitive consumer but the consensus was that reactions might be caused in exquisitely sensitive persons Penicillin may have been added illegally to lower bacterial counts but usually its presence is due to the producer s sending milk to the dairy sooner than 72 hours after treatment of the mastitic cow with the antibiotic

For several years penicillin chlortetracycline bacitracin and oxytetracycline were fed to chicks poults and swine to stimulate growth Complete tests have demonstrated no antibiotic residues in animals fed in this manner and under normal marketing conditions such use does not constitute a public health problem Chlortetracycline is also approved for use in processing poultry to extend its shelf life Three years were devoted to this study before the process was approved The evidence is conclusive that the drug cannot be found in the cooked bird—whether broiled fried boiled or baked

Antibiotics for the treatment or prophylaxis of plant diseases also constitute no health problem since none of the drugs reach the final consumer all being dissipated before the fruit or vegetables are eaten

Contamination of foods with antibiotics particularly in milk is a small problem compared to other current food safety problems related to technologic progress in food production processing and distribution especially the addition of preservatives antioxidants colors bleaches flavors coatings drying agents moistening agents thickening agents sequestering agents aging agents stabilizers emulsifiers neutralizers acidifiers and sweeteners These agents may be inherently toxic and may have an accumulative effect or combinations may have a synergistic toxic effect The problems are enormous

**Infections Complicating Gastric Surgery I Bacterial Flora of Upper Portion of Alimentary Tract and Its Re**

**sponse to Antibiotics Administered in Connection with Gastric Surgery** were studied by C F Hogman and O Sahlin[3] (Karolinska Hosp Stockholm) Antibiotic prophylaxis is routine in many departments of surgery aimed at sterilizing the stomach and upper alimentary tract before operation to prevent dissemination of bacteria at surgery Penicillin streptomycin oxytetracycline and erythromycin were tested in 76 patients with duodenal ulcer 23 with gastric ulcer 53 with gastric carcinoma and 3 with nonmalignant gastric tumor

At operation the stomach was sterile in 74% of the patients with duodenal ulcer 17% of those with gastric ulcer and 7% of those with gastric carcinoma The incidence of pathogenic bacteria in both stomach and throat was somewhat higher in the patients with cancer than in those with ulcer Oxytetracycline was administered before operation to patients with stomach cancer and 57% were sterile by the day of surgery Consequently the danger of contamination at operation in these patients was comparable to that in the ulcer group

The stomach is atonic and the acidity low immediately after resection The operative wound and the presence of blood and bile make favorable growing conditions for bacteria Bacteria from the upper respiratory tract are continually swallowed with saliva Postoperative intestinal paresis allows upward migration of intestinal bacteria The gastric flora are clearly related to throat flora and the incidence of intestinal bacteria is high in the remaining portion of the stomach Changes in throat or colon flora produced by antibiotics may be rapidly reflected in the flora of the gastric stump The throat and colon cannot be kept free from bacteria for any length of time Therefore antibiotic prophylaxis leads only to a qualitative change in the composition of the flora of the gastric stump

Oxytetracycline was given preoperatively and penicillin and/or streptomycin postoperatively to 27 patients with gastric carcinoma The mortality was 26% and half the deaths were due to bacterial complications

The postoperative incidence of resistant pathogenic bacteria in the remaining portion of the stomach was increased in patients treated with antibiotics particularly if broad

(3) Acta chir scandinav 112 1 93 1956

spectrum agents were used The bacteria most commonly seen were Staphylococcus aureus and proteus Thus postoperative infections were appreciably less amenable to therapy

**Study of Antibiotic Prophylaxis in Unconscious Patients** To evaluate the efficacy of prophylactic chemotherapy in unconscious patients in preventing infections of the lungs and skin with resistant micro organisms and the effect of antibiotics on prevalence and type of infection in patients with indwelling urethral catheters Robert G Petersdorf James A Curtin Paul D Hoeprich Richard N Peeler and Ivan L Bennett Jr[4] studied 72 unconscious patients with no overt infection admitted to Johns Hopkins Hospital from Nov 1 1955 to Feb 1 1957 Of the 72 32 were treated prophylactically with penicillin and streptomycin or tetracycline and 10 with sulfisoxazole or nitrofurantoin The other 30 received no antimicrobial prophylaxis

Mortality was uninfluenced by antibiotics Pulmonary complications developed in 45% of the prophylactically treated group in contrast with only 15% of controls Of the treated group 7 had cutaneous infections with hemolytic Micrococcus pyogenes var aureus (Staphylococcus aureus) and 2 died of bacteremia due to gram negative organisms Chemoprophylaxis did not reduce the micrococcic carrier rates Strains isolated from the treated group were more resistant to antibiotics than those cultured from controls In addition the nasopharyngeal flora were replaced by gram negative rods Routine administration of antibiotics neither prevented nor ameliorated infection of the bladder in patients with indwelling urethral catheters Resistance of the bacteria in urine did not increase during treatment but strains of other species even more refractory to antimicrobial therapy regularly appeared

Prophylactic antibiotic therapy is of no benefit and is distinctly hazardous in unconscious patients

► [Evidence such as this adds up to a convincing case against prophylactic antibiotic therapy in unconscious and debilitated patients Obviously antibiotics cannot sterilize the oral and upper respiratory passages they merely affect the normal microbial balance and favor the growth of resistant micro organisms setting the stage for infection more difficult to treat Yet we continue to hear physicians justify this practice by such remarks as Well I d sleep better if he were on penicillin —Ed ]

**Prophylactic Use of Oxytetracycline for Exacerbations of**

(4) N w E gl d J Med 257 1001 1009 N 21 1957

**sponse to Antibiotics Administered in Connection with Gastric Surgery** were studied by C F Hogman and O Sahlin[3] (Karolinska Hosp Stockholm) Antibiotic prophylaxis is routine in many departments of surgery aimed at sterilizing the stomach and upper alimentary tract before operation to prevent dissemination of bacteria at surgery Penicillin streptomycin oxytetracycline and erythromycin were tested in 76 patients with duodenal ulcer 23 with gastric ulcer 53 with gastric carcinoma and 3 with nonmalignant gastric tumor

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(3) Acta ch and ar 112 271 93 1956

**Study of Intercurrent Bacterial Respiratory Infections in Bulbospinal Poliomyelitis** John B Livingstone Frank K Austen and Lawrence J Kunz[6] (Harvard Med School) observed more than 400 patients hospitalized with poliomyelitis during the 1955 epidemic in Boston Intercurrent bacterial respiratory disease is one of the most frequent and dangerous complications in bulbospinal poliomyelitis particularly when severe enough to require tracheostomy to prevent aspiration of secretions Staphylococcus aureus resistant to multiple drugs is almost constantly present in the trachea of such patients and is the same type of organism carried by ward personnel and machinery

Combined penicillin and streptomycin prophylaxis was of no value in preventing implantation in the trachea of this drug resistant organism Despite the persistence of this bacteria in most of the patients 9 had no evidence of pulmonary sepsis and only 1 had recurrence of pneumonia after the initial infection was considered cured Chemotherapy neither prevents implantation nor readily eradicates an established organism Chemotherapy is not indicated unless sepsis is evident High prevalence of infection among patients with tracheostomy may merely reflect bulbar involvement in such degree that palatal and pharyngeal muscle weakness permits aspiration of secretions However the tracheostomy itself may increase liability to pulmonary infection

Bacteria initially associated with an episode of pulmonary sepsis were always strains of Staph aureus that were resistant to many drugs Early therapy for pulmonary infection *might be based on the antibiotic sensitivity characteristics* of the predominant strains of Staph aureus in the ward at time of the new infection Only 1 of the 119 strains tested was resistant to bacitracin in vitro and 92% were moderately sensitive or sensitive to chloramphenicol or erythromycin Therefore a combination of antibiotics theoretically effective against Staph aureus was almost always available

Because patients with pulmonary infections are unable to expel septic material from the bronchial tree they failed to respond completely to treatment with antibiotics selected according to in vitro sensitivity tests For this reason mechanical removal of secretions is as important as antibiotic therapy which is based on sensitivity studies

(6) New England J Med 257 861 866 Oct 31 1957

**Chronic Bronchitis** Exacerbations of chronic bronchitis are usually associated with proliferations in the sputum of a few species of bacteria most often Hemophilus influenzae or Streptococcus pneumoniae Since wide spectrum antibacterial drugs are effective against these organisms if given early enough they should prevent bacterial multiplication *However the drugs are too expensive for continuous use in* patients with chronic bronchitis as most patients have only one or two exacerbations each winter

A study was made between November 1954 and November 1955 by P C Elmes C M Fletcher and A A C Dutton[5] (Postgrad Med School London) to determine whether a short course of oxytetracycline at the first sign of exacerbation could decrease duration thus reducing loss of working time All patients were under age 65 regularly employed had had a productive winter cough for at least 3 years and at least 2 illnesses with purulent sputum causing loss of time from work A double blind technic was used on the 88 patients with some receiving indistinguishable dummy tablets containing lactose Neither doctors nor patients knew which tablet was which

Patients who received oxytetracycline were on the average ill two thirds as long as those who took placebo tablets and had half the number of days off work The statistical difference was not significant but the clinical impression was strong that the drug was effective in these patients Clinically the drug seemed effective in many exacerbations of bronchitis The number of H influenzae and Str pneumoniae in the sputum of these patients fell and both organisms are important pathogens in bronchitis

Only two pathogenic organisms were isolated from the sputum at the beginning of the trial or at onset of exacerbations—Str pneumoniae and H influenzae—and their presence or absence did not affect length of exacerbations Oxytetracycline banished Str pneumoniae from the sputum in every patient and H influenzae in two thirds of the patients No resistant strain of either pathogen emerged nor did any resistant Staphylococcus pyogenes appear even after several courses of oxytetracycline

► [This seems a reasonable practice The word prophylactic in the title is perhaps misleading since *the patients only had tetracycline therapy* when signs of exacerbations made their appearance —F I]

(5) Brit M J 1272 1275 Nov 30 1957

Cutaneous staphylococcic infections in hospital personnel rose sharply concomitant with development of these infections in hospital patients and fell as the patient infection rate fell These infections occurred through direct contact with the infected patient and in turn infected personnel were transmitting them to other hospital patients As soon as an infection was noted the infected person was taken off duty and treated with warm compresses and drainage if fluctuation was evident Hexachlorophene soap was used for bathing and 70% alcohol was used liberally on the involved areas and the hands Those who did not respond to these measures were given a course of novobiocin with excellent results

Cutaneous staphylococcic infections not related to surgery in 58 hospital patients were due to antibiotic resistant bacteriophage type 42B/52/81 in 76% On several occasions when furunculosis broke out in a ward one of the nursing medical or ward personnel was found to have a cutaneous infection preceding the ward outbreak from which the identical phage type organism was cultured

One of the most important means of spread of this staphylococcus is by direct contact with personnel or patients with active infection or by direct contact with heavily contaminated hospital materials Hospital and operating room technics have been relaxed during the latter years of the antibiotic era The medical profession has come to regard the problem of infection much less seriously than it did before the development of antibiotics This attitude must be changed Return to the most strict hospital technics is essential The following changes were made at the authors institution Dressing carriages were made available only with a graduate nurse in charge who was well trained in sterile technic All infected patients were dressed with a special technic in which all dressings and instruments were placed in paper bags and sterilized by steam before cleansing by supply room personnel Since strict isolation of infected patients is impractical a modified technic was developed and all bedding and clothing in contact with such patients placed in separate plainly marked bags before being transported to the hospital laundry Meticulous technic was observed in regard to hand washing and alcohol rinses by the hospital personnel after contact with infected patients Hospital per

**Bacteriologic and Clinical Experiences and Methods of Control of Hospital Infections Due to Antibiotic Resistant Staphylococci** The most significant problem with antibiotic resistant organisms is that of the staphylococcus especially in hospitalized patients Many modern institutions are infested with these organisms The true extent of this problem is unknown but it is certainly more widespread than can be ascertained from the literature Early in 1956 H Taylor Caswell Kenneth M Schreck W Emory Burnett Elsie R Carrington Norman Learner Howard H Steel R Robert Tyson and William C Wright[7] (Temple Univ ) became interested in staphylococcic infections occurring in hospitalized patients and report their findings for the first year

The staphylococcus causing severe infections was a strain lysed by 3 of the bacteriophages 42B 52 and 81 This type accounted for about 50% of all postoperative wound infections and pneumonias The same organism was responsible for 76% of the cutaneous abscesses acquired by patients during hospitalization but not related to surgery It also accounted for 80% of the typed organisms from the cutaneous infections in hospital personnel Sixteen per cent of the patients hospitalized with established staphylococcic infection were infected with this same phage type organism This strain had an extremely high percentage of resistance to penicillin streptomycin tetracycline and erythromycin

Of hospital personnel 640 were surveyed with nasal cultures and 265 (41%) were found to be carriers of a coagulase positive Staphylococcus aureus Bacteriophage typing revealed only 11 (4%) to be of the significant phage type 42B/52/81 which was responsible for 69% of hospital infections

Beginning in 1956 there was a marked rise in the number of clean surgical wounds showing infection with an infection rate of nearly 5% After institution of rigid antisepsis the rate of clean surgical wound infection fell to an acceptable level of 0 8 1 5% and has remained at that level for the past 10 months

(7) Su g Cy ec & Ob t 106 1 10 J y 19 8

penicillin in the environment The amount may be cumulative because destruction of the dried penicillin in dust may be relatively slow The penicillin would be continually redistributed through disturbances of dust and air and the handling of articles Appreciable amounts of penicillin gain access to the nares of persons working in hospital environments Without doubt this inhibits growth of penicillin sensitive strains of Staph aureus Such persons are continually exposed to recontamination with environmental staphylococci most of which are penicillinase producing strains Penicillin resistant strains therefore become easily established The environment of a factory handling penicillin was similar to that of the hospital in that it contained penicillin and all the carrier strains of Staph aureus were penicillin resistant

Environmental penicillin is an important factor in colonization of hospital nasal carriers with penicillin resistant Staph aureus and in cross infection of persons receiving or not receiving therapeutic antibiotic

**Clinical Recognition of Postoperative Micrococcic (Staphylococcic) Enteritis** is outlined by Rupert B Turnbull Jr[9] (Cleveland Clinic) This complication accounts for serious loss of life in the hospitals of the United States If unrecognized it is likely to cau e death Yet it is preventable and spectacularly curable

Some alteration or depression of the intestinal flora makes the hospital patient more susceptible to enteritis Prolonged intestinal obstruction starvation periods purging and most important administration of wide spectrum antibiotics alter bacterial antagonisms in the intestinal tract A patient is brought into a hospital environment charged with resistant strains of micrococci his normal intestinal flora are depressed or eliminated by antibiotics and the resistant micrococci are allowed to grow unopposed

Symptoms and signs of micrococcic enteritis usually appear between the 2d and 7th postoperative days The earliest signs are abdominal discomfort or pain diminished borborygmus and then abdominal distention The pulse rate rises to 120 or more the temperature rise is minimal and massive outpouring of fluid or exudate into the intestinal lumen causes diarrhea or vomiting The diarrhea consists

(9) J A M A 164 756 761 J 15 1957

sonnel with cutaneous staphylococcic infections were tal off duty as soon as infection became evident The imp tance of reporting such infections was well publiciz Measures were taken to tighten antiseptic precautions the operating room

► [An excellent example of the kind of approach which can be mad controlling the problem of hospital staphylococcic infection Phage ing showed that although a large proportion of hospital personnel v nasal carriers of coagulase positive Staph aureus only a few of t were carrying the strain which was responsible for 70% of staphyloco infections The best approach then would be to direct our effort tow isolating patients and staff members with manifest infections Attemp to treat all of the asymptomatic nasal carriers seems unnecessary as as impractical In the next article we have an interesting suggestion a one factor responsible for the frequent presence of penicillin resistant l teria in the noses of hospital personnel —Ed ]

**Environmental Penicillin and Penicillin Resistant Sta ylococcus Aureus** The proportion of penicillin resist strains of Staph aureus is increasing among carriers in h pitals who are not receiving penicillin This fact is usu explained as due to a free interchange of organisms betw *treated patients and carriers but such an explanation* p supposes that the penicillin resistant organism has power to replace the naturally occurring penicillin sensit carrier strains So far there is no satisfactory evidence t this happens

Another explanation would be that the carriers rece in their noses enough penicillin inhaled with air and d and transferred from their hands and fingers to maintai nasal concentration of penicillin inhibitory to sensit staphylococci This would be important because the antei nares are the primary site of colonization in the carrier a the staphylococci are disseminated from the nose to ot parts of the body of the carrier and to clothes the air a dust fomites and other persons J C Gould[8] (Univ of Ec burgh) sought evidence for this hypothesis by testing environment in a hospital for free penicillin and comp ing the results with those found in a factory handling pe cillin where penicillin resistant staphylococci predomina among carriers

In hospitals leakage from the phial during punctur clearing of air bubbles from the syringe spraying wl washing out the syringe insufflation of wounds with pe cillin and spilling of urine containing penicillin all lead

(8) Lancet 1 489-493 M 8 1958

purations and abscesses to chemotherapy without drainage

In 1 patient 6 weeks had elapsed and in another 5½ months between operation and clinical manifestations of infection This may represent the suppressive effect of antibiotics that were given postoperatively Apparent response to treatment with antibiotics in several patients with relapse when the drugs were stopped seems to constitute an important part of the clinical picture of this complication of cardiovascular surgery It was this clinical course that led to reoperation in 2 patients

Incidence of surgical infections is related to certain factors that include the number of persons in the operating room and agitation of air In modern cardiac surgery these factors are increased because large teams of medical personnel are required to carry out open surgery with artificial pump oxygenators

**Acute Streptococcic Myositis** (spontaneous type) is seen occasionally in the tropics but has seldom been reported in England A M Barrett and G A Gresham[2] (Univ of Cambridge) report 4 cases diagnosed at autopsy

CASE 1—Woman 33 had a cold and laryngitis One week later she had generalized malaise felt cold and shivery and had pain in the left leg The next day temperature was 103 F On admission she was restless dyspneic cold and sweaty with hypotension and fever The left thigh was edematous and hot the overlying skin was cyanotic and the urine contained albumin and acetone She was given penicillin and chlortetracycline intravenously but became moribund and died

Autopsy revealed acute suppurative streptococcic myositis of the left quadriceps femoris muscle which was pale and abnormally soft with the individual fasciculi of muscle fibers separated by thin greenish yellow pus No recent septic lesions were found anywhere on the skin Cultures from the affected muscles grew hemolytic streptococci group A type 4

CASE 2—Man 33 had severe pain in the left thigh On admission temperature was 103 2 F and pulse rate 132 he had swelling and acute tenderness of the lower anterior part of the thigh down to and including the patellar region with skin erythema The white blood cell count was 23 000 He received a total of 6 000 000 units of penicillin parenterally in the next 48 hours Under general anesthesia the lateral aspect of the left thigh was incised and pus was observed to come from the undersurface of the rectus femoris muscle Despite chlortetracycline and oxytetracycline therapy his condition worsened and he died

Autopsy revealed acute suppurative streptococcic myositis of the left thigh Cultures grew hemolytic streptococci group A, type 3

( ) L t 1 347 351 F b 15 1958

of ricewater or seawater fluid Hypotension and shock follow and the leukocyte count rises rapidly, occasionally to 60 000 *The outpouring of gastrointestinal exudate is characteristic and not likely to be confused with any other postoperative complication*

This entity might be called micrococcic cholera since the signs are so similar to Asiatic cholera The earliest symptoms and signs are not specific but other possible causes such as peritonitis and leaking intestinal anastomoses are fairly uncommon today If such symptoms do develop the diagnosis of micrococcic enteritis should be given priority since early treatment is imperative

Many pathogenic micrococci are resistant to antibiotics in general use in a locality or hospital Therefore antibiotics not in general use are more likely to be effective Erythromycin carbomycin chloramphenicol and neomycin are the drugs of choice at this time Combined oral and intravenous administration is ideal The intravenous route is used until peristalsis returns and the drug can be administered orally Erythromycin is given 500 mg intravenously followed by 250 mg every 6 hours The same dose orally should suffice The maximum dose of novobiocin intravenously is 750 mg every 8 hours with early reduction to 500 mg

► [An immediate accurate diagnosis can be made in this condition by examining a gram stain preparation of the fecal material which should be teeming with staphylococci Waiting overnight for a report on the stool culture is inexcusable —Ed ]

**Staphylococcic Infections of Heart and Great Vessels Due to Silk Sutures** Bacterial infection is uncommon after cardiovascular surgery Henry T Bahnson Frank C Spencer and Ivan L Bennett Jr[1] (Johns Hopkins Univ ) review 5 cases of postoperative infection of the myocardium and great vessels In each silk sutures represented the site of infection and definitive therapy was reoperation and removal of the foreign body A stitch abscess surrounded the silk sutures This type of infection must be recognized because of the extraordinary resistance of the infecting bacteria to antimicrobial drugs as long as the foreign body remains as a nidus Prompt cure is achieved when sutures are removed

The precise mechanisms responsible for persistence and resistance of infection around a foreign body are not known but the situation resembles the resistance of localized sup

(1) Ann Surg 146 399 406 September 1957

ingitis the inflammatory response may increase morbidity because of the increased pressure of purulent exudate before optimum antibacterial therapy is effective Evaluation of the anti inflammatory effectiveness of steroids in these cases was difficult because penicillin was given simultaneously but the remarkable decrease in cerebrospinal fluid pressure protein content and cell counts in certain patients would not appear to be attributable to penicillin alone

Whether or not the benefits ascribed to adrenal steroids in pneumococcic meningitis will be borne out in future studies it is evident that early fears related to their supposed harm in infection are for the most part unwarranted Apprehension was based mainly on the lowered resistance to latent in fections and their rapid dissemination observed after the un realistic experimental and clinical use of massive doses of adrenal hormones for long periods This study indicates that these hormones may be administered even to desperately ill patients with no increase in the incidence of untoward ef fects

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## ENDOCARDITIS AND ENDARTERITIS

**Right Sided Bacterial Endocarditis and Endarteritis Clinical and Pathologic Study** In most published review series the incidence of isolated right sided localization in cases of bacterial endocarditis is about 5% Pressure is im portant in determining the involvement of individual valves in rheumatic or bacterial endocarditis probably through local stress and trauma Robert C Bain Jesse E Edwards Charles H Scheifley and Joseph E Geraci[4] (Mayo Clinic and Found ) studied 23 cases of bacterial endocarditis or endarteritis predominantly or exclusively involving the right side of the heart or pulmonary artery which were ob served between 1911 and 1955 In 19 bacterial vegetations were confined to the right side of the heart or pulmonary artery In the remaining 4 minor vegetations appeared on the mitral or aortic valve or about the aortic o tium of a patent ductus arteriosus

Bacterial endocarditis occurs infrequently in infants and young children during the first 2 years of life In this group

(4) Am J M d 4 98 110 Ja ry 1958

All 4 patients showed acute febrile illnesses associated with pain and swelling in the muscles of a limb leading to profound toxemia with rapid feeble pulse circulatory collapse and death The patient may be young or old the pain may begin before or shortly after the constitutional disturbances None of the patients had proved septicemia However the infection probably reached the muscle via the blood because none had any history of recent penetrating wound or intramuscular injection The portal of entry of the infection into the body remains obscure

The possibility of acute streptococcic myositis should be considered if a febrile patient complains of acute pain and tenderness of the proximal part of one limb and on examination has definite swelling of a muscle perhaps accompanied by a patch of skin erythema which may not immediately overlie the site of greatest pain and swelling

Unfamiliarity with the condition is the greatest obstacle to its diagnosis

► [In view of the rapid clinical courses and fatal terminations it seems important that we be aware of this entity even though it is rare Prompt surgical drainage and chemotherapy ought to result in some saving of life —Ed ]

**ACTH and Adrenal Steroids in Treatment of Pneumococcic Meningitis in Adults** In children the incidence of recovery from pneumococcic meningitis is about 93% In adults results are less satisfactory only 50% recovering Because pressure from the inflammatory exudate might be lethal and because clinical and experimental work indicates that ACTH and cortisone suppress the inflammatory reaction to pneumococci John C Kibble and Abraham I Braude[3] (Univ of Texas) used these drugs along with penicillin in 12 patients with pneumococcic meningitis Nine were in deep coma and appeared desperately ill The usual dose of penicillin was 20 000 000 30 000 000 units daily as a slow intravenous drip Hydrocortisone and ACTH were given intravenously generally in doses of 100 200 mg of the former and 40-80 units of the latter

The recovery rate of 92% supports the concept that ACTH and adrenal steroids are beneficial in treating pneumococcic meningitis They apparently suppress two potentially harmful features of pneumococcic infection inflammatory exudation and bacterial hypersensitivity In pneumococcic men

(3) Am J Med 24 68 79 Jan ary 1958

ingitis the inflammatory response may increase morbidity because of the increased pressure of purulent exudate before optimum antibacterial therapy is effective Evaluation of the anti inflammatory effectiveness of steroids in these cases was difficult because penicillin was given simultaneously but the remarkable decrease in cerebrospinal fluid pressure protein content and cell counts in certain patients would not appear to be attributable to penicillin alone

Whether or not the benefits ascribed to adrenal steroids in pneumococcic meningitis will be borne out in future studies it is evident that early fears related to their supposed harm in infection are for the most part unwarranted Apprehension was based mainly on the lowered resistance to latent infections and their rapid dissemination observed after the unrealistic experimental and clinical use of massive doses of adrenal hormones for long periods This study indicates that these hormones may be administered even to desperately ill patients with no increase in the incidence of untoward effects

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## ENDOCARDITIS AND ENDARTERITIS

**Right Sided Bacterial Endocarditis and Endarteritis Clinical and Pathologic Study** In most published review series the incidence of isolated right sided localization in cases of bacterial endocarditis is about 5% Pressure is important in determining the involvement of individual valves in rheumatic or bacterial endocarditis probably through local stress and trauma Robert C Bain Jesse E Edwards Charles H Scheifley and Joseph L Geraci[4] (Mayo Clinic and Found ) studied 23 cases of bacterial endocarditis or endarteritis predominantly or exclusively involving the right side of the heart or pulmonary artery which were observed between 1911 and 1955 In 19 bacterial vegetations were confined to the right side of the heart or pulmonary artery In the remaining 4 minor vegetations appeared on the mitral or aortic valve or about the aortic ostium of a patent ductus arteriosus

Bacterial endocarditis occurs infrequently in infants and young children during the first 2 years of life In this group

(4) Am J M d 24 98 110 Ja ary 1958

the tricuspid valve bears vegetations almost twice as frequently as does the aortic valve Three of the 23 patients in this series were under age 2 In 2 of these a septic lesion of the skin was the probable portal of entry for Micrococcus pyogenes

The clinical course less than 6 weeks in 16 patients was of little value in suggesting the identity of the infecting organism Streptococcus viridans may cause a fulminating infection whereas usually virulent organisms may cause a lingering illness Cardiac murmurs were noted in only 8 Thus a cardinal diagnostic feature of bacterial endocarditis, namely a cardiac murmur is usually absent in tricuspid endocarditis In only 2 of the 5 patients with vegetations on the pulmonary valve was a cardiac murmur noted The spleen was readily palpable in 6 cases and questionably palpable in 2 others Petechiae were present in only 3 and clubbing was not found in any case Multiple abscesses developed in various areas supplied by the peripheral circulation in 9 cases most commonly in the subcutaneous tissue and kidneys

Blood cultures were *positive in 93%* The causative organism identified in 19 was M pyogenes in 11 Diplococcus pneumoniae in 3 Str viridans in 2 and Neisseria gonorrhoeae Str hemolyticus and Str faecalis in 1 each The marked preponderance of virulent organisms is not surprising since the frequency of right sided endocarditis is greater when virulent organisms are the etiologic agents

Evidence of pre existing rheumatic valvulitis was present in only 1 patient Congenital anomalies were present in 4 The portals through which the bacteria gained access to the circulation in 19 cases were as follows surgical procedures 10 skin diseases 3 respiratory infections 3 and prostatic massage urethritis and dental infection 1 each All but 2 cases of M pyogenes endocarditis followed a surgical procedure or a skin infection

The clinical diagnosis of endocarditis or endarteritis was made in only 6 of the 23 cases and in only 3 was the location of the vegetations *correctly diagnosed ante mortem* In none was the diagnosis made when there was no *significant cardiac murmur* The absence of a cardiac murmur and the resultant hindrance to establishment of a diagnosis in right sided endocarditis assume considerable importance

The commonest cause of death in this group was extensive pulmonary infarction and generalized sepsis

► [It is interesting that so few of these cases exhibit heart murmurs Note also that blood cultures were positive in 93% This does not support the statement frequently heard that right sided lesions may be abacteremic because of filtering of bacteria from the blood as it passes through the lungs —Ed ]

**Acquired Arteriovenous Fistula with Bacterial Endarteritis and Endocarditis** Bacterial endarteritis rarely is recognized as a cause of acquired arteriovenous aneurysm Only 13 cases have been reported in American journals In 5 of these bacterial endocarditis was also present Endocarditis without endarteritis has not been reported as a complication of arteriovenous fistula Edward W Hook Jr Howard S Wainer T Jack McGee and Thomas F Sellers Jr[5] (Emory Univ ) report 2 cases of acquired arteriovenous fistula complicated by endarteritis and endocarditis Rapid improvement followed surgical removal of the fistula combined with antibiotic therapy

Case 1 —Man 34 had a history of shortness of breath edema and temperature of 100 2 F Examination revealed a murmur He complained of pleuritic pain and temperature was 102 F Twelve years earlier he had been shot in the left thigh with a 32 caliber pistol and 2 years before admission had received another gunshot wound in the left thigh For several years he had noted a buzzing sensation in the left thigh and swelling of the left leg and thigh On admission he had splinter and fundal hemorrhages systolic and diastolic heart murmurs a pulsating mass in the lower left part of the thigh and over it a palpable continuous thrill and loud continuous murmur Fourteen of 16 blood cultures grew Micrococcus pyogenes var albus

On the 11th hospital day the left femoral arteriovenous fistula was removed A communication 1 cm in diameter joined the femoral artery and vein and showed vegetations that microscopically contained calcium and colonies of bacteria (Fig 1) He improved rapidly and became ambulatory Temperature became normal The systolic thrill and murmur at the base of the heart decreased slightly Endoarteritis in the arteriovenous aneurysm was proved and he was thought to have bacterial endocarditis evidenced by aortic insufficiency and peripheral embolic phenomena He died 1 year later probably as a result of severe damage to the aortic valve by endocarditis

Case 2 —Man 33 sustained bullet wound in the left midsubclavicular region in 1951 During this hospitalization a loud machinery like murmur was heard over the left anterior part of the chest diagnosed as traumatic arteriovenous fistula of the left subclavian artery Four years later he complained of dyspnea pleuritic chest pain fever chills and productive cough Temperature was 103 F The murmur and thrill over the arteriovenous fistula were unchanged the left arm was much larger than the right and showed extensive collateral

(5) J A M A 164 1450 14 4 July 27 1957

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in Case 1 strongly suggest endocarditis in addition to endarteritis

Attempts to control the infection with antibiotics alone have usually been unsuccessful Defervescence occurred only after the infected arteriovenous aneurysm was removed

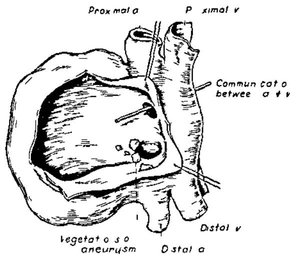
**Fungal Endocarditis Review of Literature and Report of Three Cases** Richard K Merchant Donald B Louria Philip H Geisler John H Edgcomb and John P Utz[6] (Nat l Inst of Health) review 31 previously reported cases and add 3 more 2 due to Histoplasma capsulatum and 1 to Coccidioides immitis The fungi previously implicated are candida blastomyces coccidioides aspergillus cryptococcus histoplasma and mucor Candida and histoplasma endocarditis are the most common each comprising about a third of the 34 cases

In some cases endocarditis is not clinically evident and occurs as an apparently minor manifestation of overwhelming generalized mycotic infection However most cases resemble subacute bacterial endocarditis and in these endocarditis is an important manifestation of the mycotic disease Aside from cases in which the diagnosis is readily apparent there are two clinical situations in which it should be seriously considered One involves the patient with known systemic fungal disease who has physical signs suggesting endocarditis particularly heart murmurs and evidence of major emboli Fever anemia splenomegaly etc occur commonly in systemic fungal disease without endocarditis and do not help establish the diagnosis of endocarditis The other situation concerns the patient with a clinical picture of subacute bacterial endocarditis whose routine blood cultures are sterile and who has no obvious evidence of mycotic infection Blood cultures for fungus should be obtained and a careful search made for evidence of fungal infection elsewhere by culture of urine bone marrow lymph nodes etc and adequate histologic examination of biopsy specimens Evidence of systemic mycotic infection may be an important clue to the nature of the endocardial process

As specific therapy becomes available it is increasingly important to establish the diagnosis of mycotic infection Awareness of endocarditis as a manifestation of fungal disease and the use of cultural and histologic technics to dem

(6) Ann Int M d 48 4 66 F bru ry 1958

circulation about the shoulder the heart was enlarged but without cardiac murmur and moist rales were present in the lung bases During the first 2 days of hospitalization five blood specimens were sterile On the 2d day aqueous penicillin was started 1 000 000 units every 2 hours with 0 5 Gm streptomycin twice daily Dyspnea and cough improved but fever continued On the 18th day penicillin was increased to 24 000 000 units intravenously daily On the 19th day the arteriovenous aneurysm was removed It had connected the third portion of the subclavian artery and vein A large calcified false aneurysm encased the fistula and many vascular channels connected the fistula and the false aneurysm Micrococcus pyogenes var albus coagulase negative grew in a culture of a homogenized portion of




Fg 1—Art e s u y m n m ag d 34 (Cou te y of Ho k E W J et al J A M A 164 1450 1454 July 27 1957)

the fistula although microscopic examination revealed no inflammation Fever persisted for 5 days Endarteritis was not conclusively proved in the fistula but the prompt defervescence after excision was suggestive The cultured micrococcus may not have been the etiologic agent Extensive calcification at the aneurysm site made surgical removal difficult and pathology confusing

These cases are similar to those previously reported The arteriovenous communications that were the site of endarteritis were large and involved iliac femoral or subclavian vessels Most were present for many years before endarteritis or endocarditis developed Clinical manifestations of endarteritis alone are similar to those of bacterial endocarditis except no peripheral embolic phenomena are present Nail bed and retinal hemorrhages and aortic insufficiency

overlooked until too late Lack of specific symptomatology and incon tancy of pyuria in chronic active disease is well known This problem was studied in about 2 000 persons by Edward H Kass[8] (Harvard Med School)

Urine usually is an excellent culture medium for the com mon pathogens of the urinary tract Small numbers of bac teria discharged from a renal lesion can multiply rapidly to many millions of bacteria/ml urine When infection is pres ent bacteria usually can be observed in stained specimens of urine About 100 000 bacteria/ml must be present in urine for stained specimens to be consistently read as positive Patients with more than 100 000 bacteria/ml have true bacteriuria

With this criterion for bacteriuria study of various pa tient groups at the Bo ton City Hospital revealed the fol lowing percentages of patients with bacteriuria 6% of women and 4% of men in the outpatient department 18% of women and 5% of men attending the diabetic clinic 11% of pregnant women at term 23% of women with cystocele 98% of patients with infying catheters in place for 96 hours and 2% of patients previously without bacteriuria who had single catheterization Urine was obtained by catheter in women and clean void in men Further studies showed that specimens voided into sterile containers by women and children could be used for quantitative study thus avoiding the physical and psychologic hazards of catheterization and simplifying the task of following the effect of antibacterial treatment on urinary flora The meaning of such bacteriuria is not entirely clear More than half the patients with bac teriuria by history had some past injury to the urinary tract

If a population such as pregnant women with a relatively high incidence of asymp omatic bacteriuria and pyelonephri tis is studied bacteriuria is found weeks or months before frank symptoms appear

► [Not included in the abstract is Kass s mention of the use of methionine in doses of 12 1; Gm /day in treatment of urinary tract infection The ra tionale is to shift the pH of the urine to the range of 4 5 5 0 This retards rate of bacterial grov th but rarely sterilizes the urine The main disad vantage of methionine is that some patients cannot tolerate it because of anorexia or nausea —Ed ]

**Nitrofurantoin in *Chronic Urinary* Tract Infection** The lack of an antimicrobial effect in the blood of persons receiv ing nitrofurantoin combined with marked antimicrobial ac

(8) A.M A A ch Int. M d 100 709 714 Novembe 1957

onstrate the fungi will allow the diagnosis of fungal endocarditis to be made more frequently during life

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## URINARY TRACT INFECTIONS

**Prognosis of Urinary Infections in Childhood** Duncan Macaulay and R N P Sutton (Manchester England) followed 10 boys and 22 girls treated for pyuria between 1950 and 1951 In each catheter specimens of urine had been positive Age at hospitalization ranged from 3 weeks to 4½ years and 12 were under age 1 Six boys and 21 girls could be traced Five boys with gross abnormalities of the genito urinary tract had died 2 in renal failure Of the 22 survivors 16 were re examined and 6 were studied by questionnaire to the parents and medical attendants Of the 16 examined only 8 had had no subsequent history of urinary infection were physically normal on examination and had normal urine

Despite the small number of cases some observations are relevant Urinary infection in a boy should rouse suspicion that a renal anomaly is present and an excretion urogram is indicated Of the 10 boys 7 had congenital deformities of the urinary tract Pyuria in infancy and childhood is not a simple and easily controlled condition In this small series less than half the patients who had had an attack 6 or 7 years previously subsequently remained completely well Such pyuria has sinister potentialities

► [There have been a few other studies of this nature with similar findings I agree wholeheartedly that we must take seriously acute urinary tract infection at any age Careful follow up studies to detect asymptomatic persistent infection must be arranged for See the succeeding article —Ed ]

**Bacteriuria and Diagnosis of Infections of Urinary Tract With Observations on Use of Methionine as Urinary Antiseptic** The pathogenesis diagnosis and treatment of urinary tract infections is still unsettled Pyelonephritis is the commonest disease of the kidneys found at autopsy and the active disease is noted in 10 20% of all autopsies in general hospitals The classic syndrome of fever flank pain dysuria and pyuria may be absent Pyelonephritis often occurs as a smoldering chronic infection in which diagnosis often is

(7) La et 2 1318 13 0 Dec 8 1957

Haley[1] found large numbers of fungi in the urine of 13 women and 2 men The counts ranged from 8 000 to 37 000 000 viable units/ml urine Nine patients had diabetes mellitus 3 had had surgical procedures in the preceding year and 12 had received antibiotics during this period In 9 of the 12 yeasts appeared during the course of treatment of a bacterial urinary tract infection The organisms were torulopsis and candida equally distributed in the patients without predilection for diabetics or nondiabetics Fungus infections of the urinary tract may be primary in the urinary tract or part of a hematogenous dissemination Symptoms and clinical course are indistinguishable from bacterial involvement and differential diagnosis depends on careful urine examination

## INFLUENZA

**Influenza History Epidemiology and Speculation** are reviewed by Richard E Shope (Rockefeller Inst ) The current epidemic of Asian influenza started in February 1957 in China and reached the United States about the middle of May By late July and early August it was widely seeded The symptoms consisting of fever depression anorexia and variable respiratory signs were relatively mild and lasted 2 5 days The world is being exposed to a virus with which it has had little or no previous experience

The most recent outbreak of pandemic influenza in 1918 was the most deadly ever experienced During the 4 autumn months that it prevailed it caused 21 000 000 deaths Nearly 3 times as many people died of influenza as lost their lives during the 4 years of World War I which ended just as the pandemic was passing its peak The outbreak in the spring of 1918 was the first wave of the great pandemic the immediate forerunner of the severe autumn outbreak Almost everywhere the spring wave was mild and although the morbidity was often high sometimes affecting 50% or more of the invaded population the case fatality was low The second wave in the autumn was extremely lethal and struck *simultaneously in many parts of the world In the United*

(1) Y I J B I & M d 30 9 305 F bru ry 1958
( ) Pub H lth R p 3 165 178 F b y 1958

tion in the urine defines this drug as a urinary antiseptic i e a substance likely to suppress bacteria in urine but not in tissue Ernest Jawetz James Hopper Jr and Donald R Smith[9] (Univ of California) gave nitrofurantoin to 32 out patients with chronic infections of the urinary tract For adults the initial dose was 400-600 mg daily for 1 2 weeks usually followed by a maintenance dose of 100 200 mg daily for weeks or months For children the daily dose was 100 400 mg Treatment was given either for short (14 19 days) or long (4 17 months) periods

During nitrofurantoin treatment bacteria could not be cultured from the urine in most patients but bacteriuria re curred soon after the drug was discontinued The suppres sion of bacteriuria was associated with relief from symptoms and in some instances of severe renal insufficiency resulted in measurably improved renal function Unpleasant side ef fects developed in 6 of 32 patients during the first few days of nitrofurantoin administration However ingestion of maintenance doses (100 200 mg daily) for weeks and months was well tolerated by others

Study of the patients who took nitrofurantoin for long periods showed that chronic infection in the renal paren chyma persisted despite bactericidal concentrations of anti microbial drugs in the urine and after many months of sup pression relapses promptly occurred when the drug was withdrawn In most instances the organisms recovered from the urine before nitrofurantoin treatment were so similar as to be considered identical with those isolated after months of treatment

These findings confirm the belief that a urinary antiseptic no matter how strongly antibacterial its action in the urine or how long it is taken is not likely to eradicate infection in the interstitial tissue of the kidney in chronic pyelonephritis

► [Long term suppressive therapy by urinary antiseptics or acidifying agents may be the best that can be achieved in many stubborn urinary tract infections What a false picture is given to the physician in the ad vertising matter of many of our drug manufacturers!—Ed ]

**Fungus Infections of Urinary Tract** Fungi frequently ap pear in the urine in small numbers and are usually discarded as contaminants by laboratory personnel However by quantitative culture methods significant bacteriuria or fun guria can be distinguished Lucien B Guze and Leanor D

(9) A M A Arch Int Med 100 549 557 October 1957

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(2) P b H l h Rep 73 16 178 Febru y 1958

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(9) A.M A A h I t M d 100 549 557 O t be 1957

perimental evidence has supported this hypothesis Serologic tests against swine influenza with serum samples from humans of various ages in 1935 and 1936 indicated strongly that an agent of the swine influenza virus type had been widely prevalent in man between 1918 and 1920 and not since then

A most important question now when we are in the midst of an outbreak of mild influenza which may turn out to be the first wave of a more severe outbreak is what constituted the difference between the mild first wave and the severe second wave of the 1918 pandemic By and large an attack of influenza during the mild first wave protected against infection during the more severe second wave Why then since similar influenza viruses were apparently etiologically important in each wave were the two waves clinically so different? A possible answer may lie in the bacteriologic studies The Pfeiffer bacillus appeared to be absent or of low incidence during the first wave and was almost uniformly present in the second wave

If the analogy between swine influenza and the 1918 influenza pandemic is acceptable the mild first wave of the 1918 pandemic was due to only type A virus of the swine influenza prototype The second wave was complex involving the same or an immunologically closely related type A virus plus H influenzae

In the present outbreak vaccination against the current epidemic strain is strongly indicated Full advantage should be taken of available means to protect the populace If H influenzae should happen to be important effective therapy is still doubtful Although chloramphenicol streptomycin and the tetracycline antibiotics have been effective in H influenzae infections in children the information is yet too scanty to predict how effective these antibiotics would be in treating adults especially in the event that the hemophilus was acting concomitantly with influenzae virus

► [Dozens of articles on influenza appeared during the past year describing experiences with the Asian strain of the virus in different parts of the world This excellent discussion of the history of our knowledge of influenza by a scientist who has made major contributions in the field is of special interest —Ed ]

Sudden Death Due to Fulminating Influenza occurring during a 10 day period in 3 patients is reported by D Bruce

States the height of the pandemic was the fortnight between October 12 and 26 The mortality rates recorded varied from 3 1% in New London Conn to 0 8% in San Antonio Tex Military personnel were especially hard hit During the 4 autumn months of 1918 1 of every 4 soldiers in the United States had influenza 1 of every 24 acquired pneumonia and 1 of every 67 died

Before the 1918 studies Hemophilus influenzae was generally regarded as the agent responsible for influenza Much of the investigative work was concerned with the relation of this bacterium to the disease The results were frequently confusing and contradictory which is not surprising in view of the fastidious character of the organism and the technical difficulties associated with its isolation from the respiratory tract After all these studies the role of this organism as the cause of influenza was more controversial than it was before the pandemic

At the height of the second wave of the 1918 pandemic a new disease appeared among swine in the Middle West affecting millions of swine and killing thousands The epizootic persisted in various localities until January 1919 and reappeared in the autumn and winter of 1919 as extensive and severe as it had been in 1918 It has recurred each year since then but varies annually in its severity and extent The resemblance to human influenza was striking

In 1928 the first studies of swine influenza resulted in isolation of an organism similar to the non indole producing strains of Pfeiffer s bacillus This organism was always present in cases of the disease demonstrable at sites of influenza lesions in the respiratory tract but never induced the disease when administered to normal swine Subsequently it was found that a filtrable virus differing from any hitherto known was important in causing swine influenza but the virus was not the sole cause of the influenza Both the bacterium H influenzae suis and the new filtrable virus were etiologically essential

In 1933 a virus was demonstrated to be the cause of an influenza outbreak in humans This virus was strikingly similar to that which caused swine influenza It became likely that swine had indeed acquired their infection naturally from man in 1918 and that the swine influenza virus was the surviving prototype of the 1918 pandemic virus Further ex

lungs may have been due mainly to the virus and not to pathogenic bacteria

► [Despite the fact that a fulminating clinical course is known to occur in epidemic influenza these cases seem unusual because of the paucity of symptoms compared with the massive pulmonary disease found at autopsy —Ed ]

## COXSACKIE VIRUS INFECTIONS

**Cardiac Complications of Coxsackie Virus Infection** Evan Fletcher and C F Brennan[4] (Belfast City Hosp ) report a case

Woman 28 had an influenza like illness with temperature of 100 F fine crepitations at both lung bases and an audible pericardial friction rub without murmurs Her mother who was examined at the same time had a similar illness with a pericardial friction rub and a temperature of 100 F but further study was declined and she remained at home On hospitalization the patient s temperature was 98 F The basal crepitations had cleared but the pericardial friction rub continued for 3 weeks The blood serum showed evidence of type B4 Coxsackie infection

This case of benign pericarditis was probably due to infection with Coxsackie virus subgroup B4 The symptoms lasted only a few days although the clinical signs of pericarditis persisted for weeks and the ECG was abnormal for months

Coxsackie infection may produce only minor illness which may be overlooked It should be considered as the possible cause if otherwise healthy young adults have abnormal ECG s

► [It has been suspected by a number of persons that the syndrom of benign pericarditis may be caused by infection with this virus —Ed ]

**New Syndrome of Parotitis with Herpangina Caused by Coxsackie Virus** Herpangina is characterized by grayish white papulovesicular lesions 1 2 mm in diameter with erythematous bases located on the anterior pillar soft palate and tongue J G Howlett F Somlo and F Kalz[5] (Montreal) observed 4 patients aged 19 57 who had acute parotitis associated with vesicular lesions on the oral mucous membranes from which Coxsackie virus group A was isolated The virus was demonstrated in the throat washings of all patients and in the stools of 2 by characteristic lesions produced in suckling mice

(4) Lancet 1 913 915 May 4 1957
(5) Canad M A J 7 5 July 1 19 7

Neilson[3] (Glasgow) In none was there clinical evidence of severe illness much less impending death

CASE 1—Man 22 was found dead in bed about 4 hours after returning from a dance On the previous day he had felt slightly unwell The larynx trachea and main bronchi were intensely congested and contained frothy blood stained fluid Numerous small petechial hemorrhages were evident on the pleural surfaces of the lungs which were practically airless grossly congested and edematous throughout Blood stained frothy fluid exuded freely from the cut surface All 5 lobes were an intense crimson and both lower lobes were consolidated and so friable as to disintegrate on light finger pressure

CASE 2—Man 36 had an attack of flu A few days later he was back at work apparently completely recovered On the morning of his death 3 weeks later he was at business as usual and made no complaint That afternoon pain and tightness developed in the chest and he vomited several times A second attack occurred later He went to the bathroom where he vomited and almost immediately afterward while still standing over the basin he became rigid and dropped dead Postmortem findings were strikingly similar to those in Case 1

CASE 3—Man 30 had slight breathlessness on exertion for 3 months Chest x ray showed a residual segmentary consolidation of the midbasal segment of the right lower lobe and he was hospitalized Examination revealed no signs in his chest and repeat x ray showed no change He remained well all day and had no fever In the evening he was seen by the house physician to whom he stated that he felt fine A few minutes later he arose from bed went to a sink and vomited a large amount of blood Almost immediately he collapsed and died The findings were similar to those in Cases 1 and 2

In all 3 cases the microscopic picture was similar The trachea and main bronchi were intensely congested and arterioles venules and capillaries were dilated and engorged The lungs showed widespread severe capillary congestion and many of the alveoli were filled with albuminoid fluid No virology studies were done but there can be little doubt that these are examples of fulminating influenza The pathologic changes conform to those seen during the 1918 20 pandemic It has generally been thought that most deaths in an influenza epidemic uncomplicated by underlying disease are due to secondary invasion of the lung by pathogenic organisms and not primarily to the virus Thus it was reasonably supposed that our modern armamentarium of broad spectrum antibiotics would prevent widespread fatalities in any severe epidemic These cases suggest the startling possibility that the violent hemorrhagic reaction in the

(3) Brit M J 1 4 0 42 Feb 22 19 8

meningococcemia No lesions were found in the mouth or throat

The mean cell count in the cerebrospinal fluid was 694/cu mm considerably higher than in poliomyelitis or Coxsackie meningitis in which counts above 200 are infrequent Peripheral white blood cell counts varied from 8 000 to 12 000 Recovery was uneventful The average hospital stay was 6 days (range 2 3 days)

From 94 stool preparations 58 viruses were recovered and from 48 samples of cerebrospinal fluid 15 viruses were isolated All the viruses produced the cytopathogenic changes in tissue culture The strains were neutralized by antiserum to ECHO virus type 9

Aseptic meningitis with rash is a new entity in Toronto Because of the association with a skin eruption the customary differential diagnosis of meningitis becomes somewhat restricted Conditions which may cause a similar picture clinically are rubella meningococcemia brucellosis leptospirosis and infectious mononucleosis

FREQUENCY OF CLINICAL FEATURES OF MAJOR PHASE OF ILLNE IN 115 CASES OF ASEPTIC MENINGITIS TORONTO SUMMER 19 6

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|---|---|---|
| Fever | 115 | 100 |
| Stiff neck | 106 | 92 |
| Headache | 83 | 72 |
| Vomiting | 83 | 72 |
| Rubelliform rash | 50 | 43 |
| Constipation | 46 | 40 |
| Abdominal pain | 35 | 30 |
| Cough | 23 | 20 |
| Muscle pain | 23 | 20 |

► [As described here and in the following report outbreaks of viral meningitis were observed in many European countries and North America during the past couple of years ECHO type 9 virus seemed responsible for some but not all The occurrence of an exanthem seemed variable —Ed ]

**Isolation of ECHO Virus Type 9 from Cerebrospinal Fluids** In the fall of 1956 the incidence of lymphocytic meningitis was high in Denmark but poliomyelitis was infrequent During the 7 weeks from October 30 through December 7 all cerebrospinal fluid submitted for bacteriologic examination was studied virologically Annelise Godtfredsen and Herdis von Magnus[7] (Copenhagen) studied 147 cerebrospinal fluids in tissue culture for ECHO polio and Coxsackie viruses

( ) D n h M B ll 4 233 236 D mber 1957

Besides mumps differential diagnosis includes such conditions as suppurative parotitis parotid enlargements associated with candida infections of the oral mucous membranes uveoparotid fever inclusion body parotitis and other rare conditions All these possibilities except mumps were eliminated clinically Antibodies to mumps virus did not increase The virus of herpes simplex could not be demonstrated and serum antibody titer did not rise

On the basis of clinical and laboratory findings the 4 patients were diagnosed as having the syndrome of herpangina with parotitis caused by the Coxsackie virus group A

Girl 19 had a sore throat and 4 days later a painless swelling of the left parotid gland followed by swelling of the right parotid A few herpetic lesions were noted on the left anterior pillar of the fauces She had some discomfort on swallowing and the mouth was dry The illness lasted 5 days She had had mumps 11 years earlier

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## BENIGN ASEPTIC MENINGITIS

**Outbreak of Aseptic Meningitis (Meningoencephalitis) with Rubelliform Rash Toronto 1956** is reported by R A Laforest G A McNaughton A J Beale Marin Clarke Norma Davis I Sultanian and A J Rhodes[6] Since 1949 outbreaks of meningitis in which a rash has been characteristic have been reported from various countries

During the summer of 1956 115 children were admitted to the Hospital for Sick Children in Toronto with aseptic meningitis Many more cases occurred in the city but were cared for at home Similar illnesses occurred in adults A history of biphasic illness was obtained in 42 patients The main features of the first phase were fever cold in the head vomiting diarrhea and sore throat Onset of the major phase was abrupt All patients had pyrexia and typical signs and symptoms of aseptic meningitis (table)

Most interesting was the rubelliform rash in 43% of the patients It was finely maculopapular and appeared 1 or 2 days before the major illness and persisted for 8 or 9 days It covered the face trunk and extremities In 10 patients it was on the palms and soles Three had diffuse petechiae in the skin and were admitted with an initial impression of

(6) Canad M A J 77 1-4 J 1 1 19 7

months Cerebrospinal fluid abnormalities persisted at least 5 months with 50 mononuclear cells/cu mm

CASE 5 —Man 34 had 4 attacks of meningitis within 8 years Each attack was relatively brief and without sequelae During a 5th attack a Babinski sign developed which persisted for nearly 2 months In each attack the cerebrospinal fluid protein was elevated and pleocytosis was present.

CASE 6 —Woman 49 was admitted with symptoms signs and laboratory findings of acute meningitis The cerebrospinal fluid sugar determinations suggested a bacterial infection but repeated cultures and animal inoculations were negative The meningitis was likely viral in etiology The acute phase of the illness was not unduly prolonged but the cerebrospinal fluid abnormalities were marked for a month and full recovery was not achieved until more than 3 months after onset

Besides the well recognized acute benign forms of aseptic meningitis in some instances the illness is prolonged The chronic form is probably not a distinct entity but rather indicates that varying degrees and forms of chronicity may occur including a characteristically acute and brief type of relapse with ultimate complete recovery

## INFECTIOUS MONONUCLEOSIS— UNCOMMON MANIFESTATIONS

**Splenic Rupture in Infectious Mononucleosis** Two cases are reported by Robert J Hoagland and Henry M Henson[9] (US Army Hosp Fort Benning Ga) In uncomplicated mononucleosis severe abdominal pain is rare Even moderate abdominal pain is infrequent When severe or even moderate pain develops below the left costal margin the possibility of ruptured spleen should immediately be considered especially when preceded or followed by sudden faintness or weakness The pulse rate is a valuable clue in uncomplicated mononucleosis it is almost always under 100/minute

In the past it has been considered unwise for medical students and interns to palpate the spleen excessively but a causal relation between palpation and rupture is hard to prove

CASE 1 —Man 23 had inflammation of the pharynx petechiae and *palpable lymph nodes Temperature was 101 F The leukocyte count* was 8 600 with 70% lymphocytes almost all atypical Eleven days

(9) A n I t M d 46 1184-1191 J ne, 19 7

ECHO virus type 9 was isolated from the stools of many of the patients and paired serums regularly showed a rise in antibody titer against the homologous strain As these viruses are commonly present in the intestinal tract of apparently healthy children their isolation from the stool is in itself insufficient evidence for establishing etiology ECHO virus type 9 was isolated from the cerebrospinal fluid of 21 of 104 patients hospitalized with diagnosis of meningitis or aparalytic polio In contrast no virus was recovered from 29 patients with other diseases The results strongly suggest that the illness of the 21 patients was caused by ECHO virus type 9

**Chronic Benign Aseptic Meningitis** Acute aseptic meningitis constitutes a syndrome in which the cerebrospinal fluid is bacteria free and shows a pleocytosis mainly mononuclear cells Kenneth D Bagshawe Ernest W Smith and Ivan L Bennett Jr[8] (Johns Hopkins Univ ) present 6 cases in which the course was unusually chronic but eventually benign

CASE 1—Youth 17 had relapsing meningitis with probable biologic false positive reactions to serologic tests for syphilis in the cerebrospinal fluid lasting for at least 9 months Syphilitic meningitis was unlikely because the cerebrospinal fluid complement fixation test had weakened before therapy was begun and became negative only 6 days later The blood serologic test for syphilis was weakly reactive on 2 occasions and negative on 8

In each of 2 relapses during the 9 months pyrexia grossly abnormal mental behavior headache and neck stiffness developed but all disappeared within 2 days although pleocytosis persisted Nine months after the original illness he was entirely well the cerebrospinal fluid cell count had returned to normal but the protein remained markedly elevated

CASE 2—Woman 22 had recurrent episodes of pyrexia slight neck stiffness and hypoactive tendon reflexes A cerebrospinal fluid Wassermann complement fixation test was transiently positive but reverted to negative within 20 days without specific therapy The clinical illness lasted about 1 month and was complicated by a single brief relapse and by pregnancy which went to full term with delivery of a normal child Cerebrospinal fluid abnormalities with pleocytosis and elevated protein persisted for at least 17 months

CASE 3—Girl 4 had meningitis The clinical illness was relatively brief with minor febrile relapses over 2 months but cerebrospinal fluid abnormalities persisted in the Pandy test and mastic curve more than 3 years later

CASE 4—Woman 22 had a meningitic illness lasting over 2

(8) J Ch on D 6 120 131 Augu t 1957

regions The pharynx became mildly injected without exudate Heterophil agglutination at this point was 1 3584

The manifestations of pericarditis in this case preceded signs of infectious mononucleosis by a full week a sequence noted in other reported cases This fact together with the mild course of the infectious mononucleosis which ensued could easily cause the diagnosis to be overlooked in other similar cases

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## TUBERCULOSIS

**Hematogenous Infection of Closed Fractures with Mycobacterium Tuberculosis** Panayiotis Smyrnis (Sea View Hosp New York) reports 3 cases in which fractures occurred through undiseased areas of the proximal portion of



F g (l ft) —Roe tg g m t t m f f t
F g 3 ( ght) —S m th ft jury
(C rt y f Smy P J B & J t S g 39A 90 904 J ly 1957 )

the femur In 2 reduction and internal fixation of the fracture resulted in healing In 1 no surgery was required but months later the fractured area was found to contain tuberculosis Tuberculous infections of bones and joints result from metastatic spread through the blood stream from a

( ) J B & J t S g 39 A 90 904 J ly 1957

later he vomited had three loose defecations and felt faint The next morning the abdomen was diffusely although only slightly tender Pulse rate rose to 96 then to 112/minute and abdominal pain increased The next day pain in the left hypochondrium was severe hemoglobin had dropped to 9 9 Gm / 100 ml and hematocrit to 33% An emergency operation on that day revealed a large subcapsular hematoma and about 1 200 cc free blood in the peritoneal cavity The spleen was removed

CASE 2—Man 25 had pain in the left upper quadrant for 4 days The pharynx was moderately inflamed pulse rate was 84/minute the left upper quadrant was slightly tender and the leukocyte count was 9 000 with 63% lymphocytes many atypical Six days later the abdominal pain which had partially subsided worsened and increased the next day Splenic rupture was diagnosed when the mucous membranes were noted to be excessively pale Hemoglobin was 5 7 Gm / 100 ml and hematocrit 18% Splenectomy was performed Blood volume was estimated at about 3 000 cc A rent was found in the capsular area near the inferior pole of the spleen The postoperative course was uneventful

► [Since early surgical intervention may be essential we must keep this rare but very serious complication in mind when dealing with an ordinarily benign illness —Ed ]

**Acute Pericarditis as First Manifestation of Infectious Mononucleosis** Acute nonspecific pericarditis which sometimes follows an upper respiratory infection is characterized by anterior chest pain of pericardial origin often with a pleuritic component which may be influenced by position The cardiac silhouette commonly is moderately enlarged attributed to a small pericardial effusion Pleural effusion may also occur Electrocardiograms show the typical evolution of acute pericarditis In the past 9 years 8 cases of acute pericarditis associated with infectious mononucleosis have been reported David M Roseman and Richard M Barry[1] (Cornell Univ ) report another

Man 26 had headache and myalgia for 3 days Severe crushing substernal chest pain with radiation down the left arm had awakened him from sleep on the morning of admission No pericardial friction rub was heard The white blood cell count was 5 400 and atypical lymphoid forms were not seen The ECG showed typical acute pericarditis and heterophil agglutination was borderline positive in a dilution of 1 128

He was treated with bed rest without antibiotic therapy and became afebrile and free from chest pain in 5 days No friction rub developed The cardiac silhouette remained normal On the 5th hospital day the differential white blood cell count showed 70% lymphocytes of which half were atypical *On the 7th day tender enlarged lymph node* developed in the cervical epitrochlear axillary and inguinal

(1) Ann Int Med 47 351-356 Aug t 1957

**Treatment of Tuberculous Meningitis Comparative Trial** by a Scottish joint committee is reported by T Anderson[4] (Univ of Glasgow) The trial was undertaken because of the desire to eliminate intrathecal streptomycin therapy if this were no longer necessary Patients were followed for a minimum of 21 months The total series consisted of 111 patients allocated at random to three treatment groups 30 in the standard group who were given streptomycin intramuscularly and intrathecally PAS orally but with isoniazid withheld at least for the first 8 weeks 43 in the isoniazid group who also received PAS daily throughout the therapy period and 38 in the compromise group who were treated the same as the isoniazid group for the 1st week but thereafter still receiving isoniazid and PAS were given intramuscularly and intrathecally 2 doses streptomycin weekly Treatment was continued for at least 6 months in each group The three groups were not identical but severity of the meningitis was equivalent

There were 21 deaths a mortality rate of 19% of which 8 were in the standard group 6 in the isoniazid group and 7 in the compromise group Results were satisfactory in the isoniazid and compromise groups in total mortality and the mortality in the first 28 days of treatment Results indicate that when isoniazid was included in the chemotherapy intrathecal streptomycin was not essential Reduction of intrathecal therapy is rational

**Adrenal Corticoids in Treatment of Tuberculous Meningitis** Ole Wasz Hockert[5] (Univ of Helsinki) reports studies including 2½ years follow up on a series of 37 children who received corticoids as compared to 37 others who received the same treatment except no corticoids Hydrocortisone was given intrathecally 1 mg /kg together with streptomycin and isoniazid for 3-4 weeks Cortisone was given in 3 divided oral dose daily for about 2 months

The main problem in tuberculous meningitis is the presence or occurrence of high blocks that occlude the narrow passages in the brain Low blocks in the cerebrospinal canal usually are easily handled Use of steroids apparently prevents occurrence of high block during treatment This cannot be proved statistically unless a larger series of patients is

(4) Lan t 2 756-760 O t b 19 1957
(5) Ann pa d t F 3 90 96 1957

primary complex in the chest or lymphatic glands Such metastases must seed thousands of locations within the body at one time yet only a few develop into destructive lesions Multiple bone and joint lesions should be expected yet solitary lesions are usual

Man previously had many admissions for alcoholism and pulmonary tuberculosis The right leg had been amputated traumatically in 1924 In 1955 he fell and fractured the right femur (Fig 2) It was reduced and fixed internally Because of the pulmonary tuberculosis he was admitted to a sanatorium but remained ambulatory on crutches Four months after the fracture he complained of pain and stiffness of the right hip Because of the pain the internal fixation was removed and a large tuberculous abscess was found (Fig 3) Antituberculosis therapy was begun Subsequently the skin incision healed and the process subsided

In presence of tuberculous bacteremia severe trauma such as a fracture may lower tissue resistance and allow implantation and growth of tubercle bacilli This does not imply that all instances of bone and joint tuberculosis are localized by antecedent injury The conditions for such localization are specific

**Treatment of Tuberculous Meningitis with Combination of Isonicotinic Acid Hydrazides Streptomycin and Para Aminosalicylic Acid** in 41 patients between 1952 and 1956 is reported by Emanuel Appelbaum and Charles Abler[3] (New York) Age range was from under 1 year to 64 with predominance of younger patients Over half were treated within 2 weeks of onset The Mantoux test was done in 30 cases and in 28 it was positive

Treatment in most was 10 mg/kg body weight isoniazid streptomycin 1 Gm and PAS 6-12 Gm daily Some received 14 18 mg/kg body weight on several occasions Of the 41 patients 12 died 4 of whom were moribund on admission and were treated for only 4-10 days before death Marked muscular spasticity and mental retardation developed in 3 patients and 1 of these also had optic atrophy The 29 survivors have been observed for 4 months to 4½ years and at present most are in good general physical condition and have normal mentality

► [Twenty nine recoveries among 41 cases including all age groups seems a fairly accurate picture of what can be accomplished with present day chemotherapeutic agents —Ed ]

(3) A n I t M d 47 782 793 October 1957

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(4) La t 2 756-760 Oct be 19 1957
(5) A p d t F n e 3 90 96 1957

studied but no blockage occurred in those patients who received steroids during treatment

Hydrocortisone when given intrathecally did not recanalize existing adhesions but did prevent their occurrence This is understandable from its effect in suppressing inflammation

Theoretical studies and long term clinical experience favor adjuvant treatment with steroids for patients with tuberculous meningitis Today therapy is simplified isoniazid and cortisone are given routinely in early cases and for more severe cases streptomycin is added In advanced cases hydrocortisone is given intrathecally Streptomycin need not be injected intrathecally in most patients because isoniazid is so effective

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## FUNGOUS INFECTIONS

► An unusually large proportion of this year s selections deals with fungous infections Their relative importance and perhaps their frequency seems to be increasing Amphotericin B is the best antibiotic so far available for this group of infections —Ed

**Pulmonary Actinomycosis** The need to recognize all forms of infection has become most important since pulmonary involvement may be mistaken for carcinoma of the lung and because current therapies with various antibiotics although frequently of prolonged duration are now curative During the past 3 years Thomas A Warthin and Boris Bushueff[6] (Harvard Med School) have encountered 3 patients with proved pulmonary actinomycosis Two were hospitalized with a presumptive diagnosis of carcinoma

The central location of the lesion was interesting and was in accord with previous descriptions of early pulmonary actinomycosis Each patient was in the age group in which carcinoma of the lung is of considerable concern and all had long histories of cigaret smoking Adequate fungus studies were made on only 1 patient but the diagnosis probably could have been established in the other 2 without surgery if cultures had been taken before surgery

The x ray findings in the 3 cases were sufficiently similar to enter into the differential diagnosis of pulmonary lesions An area of fan shaped consolidation was seen near the hilus

(6) A M A Arch Int Med 101 239 243 February 1958

or radiating from it usually posterior and frequently involving the apical segment of a lower lobe This finding may not easily be differentiated from the usual appearance of neoplasm or pneumonia If definitive bacteriologic findings are absent the possibility of pulmonary actinomycosis should be considered Patients suspected of having carcinoma who show the aforementioned x ray signs with suggestive lymph node involvement should have a careful smear and culture of their sputum for actinomycosis before surgery

**Cave Disease**—Geoffrey Dean[7] (Port Elizabeth South Africa) reports a case

Man spent an entire day underground investigating deep caves which contained large quantities of bat guano in places the guano was over 8 ft deep Thousands of bats the common small variety and a larger type with a wingspan of over 3 ft occupied the cave Twelve days later he had a burning sensation across the chest headache and fever that progressively worsened until he was unable to take a deep breath without coughing He appeared to have bilateral pneumonia Three weeks after onset he was desperately ill with cyanosis rapid and shallow breathing medium crepitations throughout the lungs and a pleural rub at both bases The white blood cell count was 12 000 with 90% polymorphonuclears X ray study revealed wooly opacities scattered throughout the lungs most marked at the bases The complement fixation test for psittacosis was negative The histoplasmin skin test was positive although complement fixation was negative Over the course of a month symptoms subsided and physical signs disappeared although he still complained of lassitude

Similar cases have occurred among cave explorers in the Transvaal The so called curse of the Pharaohs may be cave disease This curse was said to be responsible for the deaths of many archeologists connected with the opening of the tomb of Tutankhamen Lord Carnavon s death from pneumonia 6 weeks after opening the inner sanctuary of the tomb started the superstitution which was given great publicity by the world press at the time The author s theory is an interesting possibility but still requires investigation

**Sporotrichosis Report of 23 Cases in Upper Extremity** is presented by Robert J Duran Mark B Coventry Lyle A Weed and Robert R Kierland[8] (Mayo Clinic and Found ) This infectious granulomatous disease of fungous origin is most common in an upper extremity and is rarely reported in bones joints muscles central nervous system and viscera If diagnosed it can usually be cured if unrecognized

(7) C t l Af n J M d 3 79-81 M h 1957
(8) J Bon & J nt Su g 39 A 1330 134 Dec mb 1957

it spontaneously regresses and results in chronic disability To some extent it is an occupational disease often occurring among people who work with soil and vegetables

Of the 25 cases 21 began as the localized lymphatic type and 1 progressed to the systemic type In 11 patients the dis

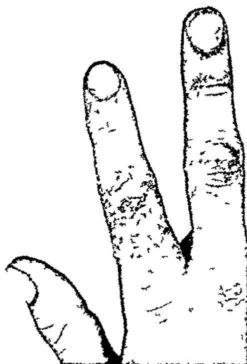


Fig 4—Primary lesion on dorsal surface of index finger Pustule has ruptured and ulcerated (Courtesy of Durham R J et al J Bone & Joint Surg 39 A 1330 134 December 1957)

ease occurred on the dorsal or volar aspect of the hand The cutaneous form is characterized by ulcers nodules gummas and abscesses From 20 days to 3 months may elapse after inoculation before appearance of the primary lesion which may begin as a small abscess at the site of trauma (Fig 4) Commonly within a few days to a week the fungus spreads through the lymph channels to produce an ascending chain of secondary subcutaneous nodules Lymph channels may appear as firm cordlike painless structures The nodules are freely movable and painless and later become attached

to the skin They may soften and ulcerate discharging a thin watery secretion (Figs 5 and 6) and may persist for months or years if untreated Usually in the localized form general health is unaffected

Histopathologic appearance is similar to that of other granulomatous diseases Organisms usually are not found



Fig 5 (top) —P imary les on on radial aspect d tal ph l x of right ind x fing w th mult pl e ond y od l a d ul e s on f rea m d rm Th cl n cal p t e ll t tes loc l d lymph typ

Fig 6 (bott m) P m y l on n d s m f h d w th multipl ul at e a d dula ond y l on d um a d f e rm T pic l t lo alized lymph t c typ

(Court y of D a R J J J Bone & J nt S rg 39 A 1330 134 December 1957 )

Accurate diagnosis rests entirely on isolation of the organism Sporotrichosis is a chronic illness with cutaneous or subcutaneous nodular lesions suggesting lymphatic dissemination but without the usual inflammatory signs of bacterial infection Potassium iodide is the drug of choice for treating the localized lymphatic form and all other forms except those involving the central nervous system The patient with sys

temic involvement presents a more serious and perplexing problem

**Hypoparathyroidism and Moniliasis** Clinical factors that appear to promote moniliasis are (1) general malnutrition which is particularly likely to promote oral infections (2) diabetes mellitus which may predispose to moniliasis in the vulva and vagina (3) chronic infections particularly if resistant to multiple antibiotics (the antibiotic may be blamed but malnutrition consequent to the infection may be a factor and the tissues devitalized as a result of the original disease) and (4) hypoparathyroidism

D K O Donovan[9] (Univ College Dublin) observed 14 adults with chronic postoperative hypoparathyroidism In none did clinical evidence of moniliasis develop although for many years they had been inadequately treated In 2 cataracts developed Also observed were 4 children with hypoparathyroidism in whom symptoms of moniliasis were striking Perhaps the enhanced resistance in adults is due to some immunity developed from infections in earlier years Moniliasis in children with hypoparathyroidism reveals the more subtle symptoms of chronic infection associated with increased susceptibility All 4 children gave a history of repeated episodes of oral thrush with a steady decrease in frequency as they grew up All had well marked moniliasis of the fingernails None continued having active chronic moniliasis of the skin all skin lesions ultimately cleared with increasing age and normal blood calcium

Hypoparathyroidism predisposes to moniliasis in children but not in adults This may be a function of the patient s general nutrition The clinical picture of chronic moniliasis is variable and not obvious It may present as malabsorption laryngitis or bronchitis Lesions on the nails may be more obvious In chronic cases the skin lesion is not obvious

**Genitourinary Blastomycosis Case Report and Review of Literature** are presented by Donald Rolnick and George O Baumrucker[1] (VA Hosp Hines Ill)

Man 53 had osteomyelitis which required a below knee amputation Blastomycosis was found in the bones of the right foot Two months later he was hospitalized with a 2 day history of acute urinary retention He had had no previous urinary complaints A chest x ray revealed blastomycotic involvement of the lungs He became febrile and multiple cutaneous lesions developed Blastomycosis was con

(9) I h J M Sc pp 255 57 J 1957
(1) J U ol 79 315 3 3 F bru ry 1958

firmed by prostatic smear and culture and biopsy of a cutaneous lesion He was treated with stilbamidine and iodides and the cutaneous and pulmonary lesions cleared

Four years later he was readmitted with a 2 day history of marked dysuria Examination revealed a firm nodular nontender enlargement of the left epididymis and a soft boggy tender prostate Greenish yellow purulent material was expressed from the prostate on massage which contained small round doubly refractile bodies typical of blastomycosis Antibiotics did not relieve the dysuria Left orchiectomy was done The pathologic report showed blastomycosis of the epididymis but culture was negative for blastomycosis A transurethral resection biopsy of the prostate gland revealed chronic prostatitis with no evidence of blastomycosis A second course of stilbamidine therapy in the form of 2 hydroxystilbamidine was given At the time of discharge he had no urinary complaints and prostatic smears were negative for blastomycosis

In treatment of genitourinary blastomycosis 2 hydroxystilbamidine has replaced stilbamidine because it is more stable and less toxic It does not cause trigeminal neuralgia which is the most distressing toxic effect of stilbamidine The dose of 2 hydroxystilbamidine varies from case to case but is usually 5 15 Gm given intravenously by slow drip

**Treatment of North American Blastomycosis with Amphotericin B** Stilbamidine and 2 hydroxystilbamidine are not effective in curing all cases of systemic North American blastomycosis though most patients have benefited from such therapy Relapse after proper administration of the stilbenes apparently develops in patients who show immunologic status of a negative blastomycin skin test and a persistently positive complement fixation test Such patients have the poorest prognosis

E Richard Harrell and Arthur C Curtis (Univ of Michigan) treated 4 patients with systemic North American blastomycosis resistant to stilbamidine with a new antibiotic amphotericin B known to have antifungal properties in vitro Amphotericin B was administered as a suspension of the non water soluble drug containing a particle size of $5\ \mu$ or less Because of this the solution (50 mg amphotericin B/1 000 cc of 5% dextrose in distilled water) was frequently agitated and filtered through the common type of filter such as used during whole blood transfusion and was given intravenously as a slow drip over 6-8 hours

All 4 patients had pulmonary and cutaneous disease and 2 had destructive osseous and 1 prostatic involvement All 4

( ) A M A A h D m t 76 561 569 N mb r 19 7

had identical immune responses—a persistently positive complement fixation test and a negative blastomycin skin test—indicating poor prognosis Response to intravenous *amphotericin B was favorable (Figs 7 and 8) in all and*



Fig 7 (left) —Rec t e t e e t les ns of f e that d l ped after 25 425 Gm hyd o y t lb m d e d/ t lb m d
F 8 ( ght) —C mpl t heal g f ta eou l on 1 month afte mphot ric n B th rapy wa t ted
(C t sy f Ha r ll E R a l Cu t A C A M A \ch D mat 76 561 569 N mbe 1957 )

much more rapid than that to the stilbamidines Fungi were completely eliminated from the sputum and the cutaneous lesions healed rapidly The optimal daily dosage is unknown but this initial experience is most encouraging

► [The immediate response to therapy seems impressive indeed but in view of the ability of this micro organism to persist in tissues long term observation will be required before it can be ascertained whether perma nent cure has been achieved The drawbacks of amphotericin are that se vere toxic effects may be encountered and that it has to be given daily by slow intravenous drip for weeks at a time —Ed ]

**Cryptococcus Meningitis Arrested with Amphotericin B** A case is reported by Emanuel Appelbaum and Sinovij Shtokalko[3] (New York) The tendency toward spontaneous remissions in this disease makes evaluation of drugs difficult In this case the marked sensitivity of the isolated organism to the drug and the pronounced clinical and cerebrospinal

(3) A n. I t M d 47 346 351 A g st 1957

fluid improvement after parenteral therapy was started suggest the drug was effective The time since termination of therapy is insufficient to allow final appraisal of the drug

Woman 46 had headache and stiffness of the neck of 2 months duration She had had diabetes for 20 years The cerebrospinal fluid was clear but contained 120 cells and cultured Cryptococcus neoformans Oral amphotericin B was started with 1 6 Gm and increased progressively to 8 Gm daily Despite intensive treatment she deteriorated markedly After 5 weeks of oral treatment parenteral therapy began as 100 mg amphotericin suspended in 500 cc of 5% glucose in saline given slowly intravenously over 6 hours once daily for 12 days then every 2d day for 5 weeks Within 2 weeks she improved particularly in clearing of the sensorium Improvement was progressive with defervescence and recession of neurologic signs and symptoms At discharge she was in good physical and mental condition asymptomatic and she remained so at follow up 7 months later

During administration of amphotericin B renal function seemed to be transitorily impaired as evidenced by increased blood urea nitrogen

► [Here again final verdict must be withheld but several similar encouraging results have been obtained An effective treatment for torula meningitis will be a real victory —Ed ]

**Coccidioidomycosis and Its Treatment with Amphotericin B** Coccidioidomycosis is one of the most important of the primary systemic mycoses particularly to residents and visitors of southwestern and western United States Even limited exposure to infected dust during brief travel through an endemic area may cause infection Skin tests have shown that 10 15% of new residents in endemic areas contract the infection within the 1st year and about 90% within 10 years The disease varies from asymptomatic or mild influenza like pulmonary infection *called valley fever to fatal progressive* and disseminated granulomatous disease (coccidioidal granuloma)

In the past primary treatment was prolonged bedrest the same as advocated for pulmonary tuberculosis before specific antibiotics became available Surgical extirpation of the pulmonary residua of infection was done to prevent dissemination of the disease Specific chemotherapy for disseminated coccidioidomycosis however was not available and prognosis in this form was poor

At present attention is focused on amphotericin B a polyene antifungous antibiotic M L Littman Phillip L Horowitz and J G Swadey[4] (New York) report beneficial

(4) Am J M d 24 568 59 Ap 1 1958

clinical effects in 4 patients when the drug was given intravenously. Maximum tolerated intravenous dose was 1.16 mg./kg./day when given in glucose solution over a 6-8 hour infusion period. An intravenous dose of 28 mg. given with glucose within 40 minutes proved almost fatal in 1 patient, causing acute prolongation of the Q-T interval in the ECG, severe depression of cardiac conduction and cardiac standstill, which in this case was reversed. In doses of 1.16 mg./kg./day over 6-8 hours, the drug induced no cardiac toxicity.

Side effects such as nausea, occasional vomiting, flushing, perspiration, fatigue, drowsiness, chilliness, febrile reactions, anxiety and generalized pain subsided when the drug was stopped. Febrile reactions to 102 F. were common but could be controlled by prophylactic salicylates or antihistamines. Toxicity from amphotericin B primarily involved the kidney and in almost every instance of excessive or too frequent dosage, rising azotemia occurred. Infusions were discontinued when the blood urea nitrogen exceeded 30 mg./10 ml. or nonprotein nitrogen exceeded 50 mg./100 ml., and not restarted until the azotemia was alleviated. Liver function, hemopoiesis and the neurologic system were not affected deleteriously.

► [Results obtained in California in severe forms of disseminated coccidioidomycosis have not been so encouraging.—Ed.]

## PARASITIC INFESTATIONS

**Trichinosis Involving Central Nervous System: Treatment with Corticotropin (ACTH) and Cortisone.** When trichinosis involves the central nervous system, the symptoms may be nonspecific, such as headache, neck pain, stiffness, apathy, confusion and decreased reflexes, or there may be specific focal cerebral damage in which the mortality is as high as 34%. Lawrence E. Meltzer and Albert A. Bockman (Philadelphia Gen'l Hosp.) describe a patient with clearly defined focal cerebral damage due to trichinosis. Combined steroid therapy rapidly reversed the neurologic signs.

Man, 43, had headache, malaise and fever which had been treated

(5) J.A.M.A. 164:1566-1569, Aug. 3, 1957.

with penicillin On admission temperature was 101 103 F He was confused disoriented semistuporous and unable to use his left hand He had splinter hemorrhages under all fingernails Neurologic examination showed wristdrop inability to abduct or adduct the fingers and weakness of the flexor muscles of the upper and left lower extremities The plantar response was extensor bilaterally abdominal reflexes were absent The diagnosis was poliomyelitis

The results of the lumbar puncture were normal The white blood cell count was 15 500 with 50% eosinophils Further history revealed the ingestion of raw pork A muscle biopsy showed no parasites A skin test was negative on April 24 but markedly positive on May 14

Therapy consisted of 300 mg cortisone with 80 units of corticotropin daily This was reduced to 200 mg cortisone and 60 units of corticotropin for 3 more days Maintenance doses of prednisone in decreasing amounts were given for the next 10 days Within 24 hours of the start of therapy the temperature became normal and improvement was striking He cleared mentally in 48 hours Muscle strength was first noted in 5 days and became normal in 13 There were no sequelae

The dramatic clinical improvement in this patient after steroid therapy was considered related to an antigen antibody response Steroid therapy is indicated early in the course of the disease

► [Severe trichinosis is an ideal situation for steroid therapy the parasite is incapable of continued multiplication in this host and there is good reason to regard some of the clinical manifestations as resulting from hypersensitivity to the parasite We too have seen steroids produce dramatic improvement in cerebral trichinosis —Ed ]

**Cranial and Cerebral Hydatid Disease** This condition is usually associated with raising sheep and cattle and occurs mostly in Australia North Africa South America Iceland and Southern Europe It is caused by invasion of the brain by Taenia echinococcus Infection occurs by contamination of food with dog feces containing echinococcus segments On reaching the intestinal tract the ring liberates eggs the hexacant embryos leave the eggs and pass through the intestinal wall ultimately reaching the lung liver and sometimes the brain in which organs hydatid cysts may develop Among 2 226 intracranial space occupying lesions operated on between 1935 and 1955 C Arseni and D C Samitca[6] (Postgrad Inst of Medicine Bucharest) found 36 intracranial and cranial hydatoses

Usually the cyst is unilateral It may reach the size of an orange and is well separated from the brain tissue which is merely dislocated *in the same way as a meningioma The* neurologic signs may be reversible if compression has not

(6) Act psych et neurol scand 32 389 398 1957

been present too long In 3 of the 36 patients hydatid cysts occurred elsewhere in the body Meningeal and cerebral hydatosis gives rise to signs of increased intracranial pressure Headache was present in 59% headache and vomiting in 36 5% choked disks in 50% and secondary optic atrophy in 10% Neurologic findings were minimal and depended on localization of the cyst Some patients showed increased tendon reflexes hemiparesis mental disturbances frontal syndrome disturbances in speech or in cranial nerves (espe



Fig 9—R nd w ll d d t (C u t y f A n C nd Sam t D C Acta p y h t et n u ol sc d 32 389 398 1957)

cially the 6th) or cerebellar dysfunction Epilepsy occurred in 50%

The blood picture is usually diagnostic Pneumoencephalography may be performed in patients with no signs of intracranial pressure If the cyst should happen to be punctured (80% of the author s patients) it results in cystography with either a spheric or ovular cyst (Fig 9) The appearance of a cyst with a double contour is pathognomonic for cerebral hydatosis Should the cyst contain daughter cysts they are seen as *small spherules on the inner side of the cyst* Cerebral hydato is should be suspected when a child or a young adult dwelling usually in a rural area shows

signs of increased intracranial pressure mild neurologic signs and focal epileptic seizures and perhaps harbors hydatid cysts elsewhere in the body The only effective treatment is surgical extirpation

Cysticercosis Cerebri—Cestode Infestation of Human Brain Report of Case Occurring in Louisiana According to John H Dent[7] (Tulane Univ ) pork tapeworm larvae are rarely found in the central nervous system of human beings in the United States and Canada but are prevalent in South America and in the Far East Cysticercosis is caused by larvae of the cestode Taenia solium Man may become infested by ingesting material contaminated with egg laden feces The eggs hatch in the upper small intestine the larvae penetrate the intestinal wall enter the lymphatics and blood vessels then become widely and fortuitously distributed and develop into cysticerci at the site of localization The body wall of the larva proliferates the center liquefies and a cavity forms A scolex develops and invaginates into the pre formed cavity The cyst reaches full size of about 1 cm in diameter in about 10 weeks The skeletal muscles chambers of the eye and the central nervous system are most often affected In skeletal muscle fibroblasts proliferate and surround the cyst by a fibrous capsule eventually calcifying Within the central nervous system the larvae may be localized within the leptomeninges or brain substance The racemose type of cysticercosis develops in the leptomeninges overlying the brain stem and cerebellum Projections of the cyst may extend as much as 15 cm Within the brain parenchyma individual lesions seldom exceed 1 cm in diameter They may cause epilepsy

As long as the larvae live the inflammation provoked is only minimal Death of larvae however produces intense local granulomatous inflammation in the leptomeninges with foreign body giant cell reaction and fibrosis Focal or localizing clinical signs are rare Increased intracranial pressure papilledema headache nausea and vomiting mental deterioration and personality changes are common in advanced stages of the parenchymal and racemose types of central nervous system inflammation

Man 44 farmer had regressive personality changes steadily increasing in severity for 3 years slowly developing muscular weak

(7) J A M A 164 401 405 May 25 1957

ness of the lower extremities urinary incontinence and headache Examination revealed papilledema generalized mild ataxia and muscle weakness slight facial weakness and minimal pupil inequality Intraventricular pressure was greatly increased At craniotomy no tumor was found He died after a second craniotomy Autopsy revealed the leptomeninges in the region of the peduncles to be thickened and to contain many small cysts Many cysts were found in the brain parenchyma Histologic changes were consistent with those in cysticercosis

**Pulmonary Ascariasis** A case is reported by A K J Koumans[8]

Woman 60 had mild respiratory infection She had been ill with



Fig 10 —M t d t fied s Glyc ph gu found sp t m f woman (C urt y f Koum n A K J Ned l t jdsch g n k 101 112 11 4 J 15 1957)

grippe for 5 weeks with attacks of coughing temperature to 101 F slight congestion and vague pains in the chest had been bedridden 4 weeks and had not responded to usual treatment The chest sounds were those of spastic bronchitis There were no signs of cardiac decompensation Pale whitish turbid sputum contained many leukocytes (a high proportion of eosinophils) and small rust brown flecks that microscopically appeared pale in the presence of erythrocytes Gram staining showed a banal flora with no acid fast bacilli There was no anemia the leukocyte numbered 8 800 (29% eosinophils) Prothrombin time was normal The ECG showed slight but insignificant changes There was no history of allergy Stool examination showed no worms or parasites The chest x ray showed some calcified plaques but no signs of tuberculous activity Some fresh infiltrate in the left middle field suggested atelectasis

Repeated sputum examinations finally yielded male and female

(8) N d l t jdsch g ee k 101 1122 1124 J e 15 1957

mites 1 pair was moving freely In 14 daily examinations parasites were found in 8 specimens The mites were identified as Glyciphagus Their average size is 226×147 μ (Fig 10) and they are found in various substances including house dust Infection results through inhalation

Establishment of this mite in the epithelial wall of the respiratory tract accounted for the bloody sputum the mild secondary infection and the eosinophilia that presumably—as well as the transient infiltrate—were related to an allergic reaction against the parasitic invasion

The fever was reduced by treatment with bed rest Achromycin® and sulfamezathine and after administration of Stovarsol the cough and expectoration gradually decreased as the parasites became fewer and less active After 4 weeks the patient was clinically cured and the eosinophil count had decreased to 9%

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## MISCELLANEOUS ENTITIES

**Brain Abscesses Review of 99 Cases** is presented by Eugene Loeser Jr and Labe Scheinberg[9] (Columbia Univ Presbyterian Med Center) These cases were seen during 1940-56 and were divided into three 5 year periods corresponding to the years in which sulfonamides penicillin or broad spectrum antibiotics were commonly used The patients were aged 9 days to 68 years and males predominated 2 1 The increased risk of trauma in males explains only a small proportion of this preponderance

In 26% an abscess was present without evident of previous infection Perhaps the infection had been suppressed by antibiotics or chemotherapy The site of brain abscess has not changed since the introduction of antibiotics A high proportion (25%) of the abscesses were sterile Pneumococcus has declined in frequency from abscesses cultured since 1944 with an increase in the occurrence of Streptococcus viridans

The clinical course from the time of primary infection to the first symptom of intracranial involvement ranged from 2 months to over 20 years Once neurologic symptoms developed the course was rapidly downhill Temperature and pulse rate on hospitalization were of little value in indicating a suppurative process The white blood cell count and erythrocyte sedimentation rate were elevated in two thirds to three fourths of the patients The cerebrospinal fluid count

(9) N 1 gy 601 609 S pt mbe 1957

was 5 or less in 21 patients and there were over 1 000 white blood cells/cu mm in 14 The protein level was elevated in 48 of 61 examinations The sugar level was under 40 mg/100 ml in 9 patients 8 of whom also had over 1 000 white blood cells/cu mm

Roentgenograms were abnormal in half the cases showing pineal shift erosion or increased intracranial pressure The EEG revealed localizing or lateralizing features in 29 of 41 examinations

The average surgical mortality in the 99 patients was 37% with successively better operative results in later years Results improved when penicillin was introduced and again when broad spectrum antibiotics were brought into use The best results were obtained with a combination of sulfonamide penicillin and broad spectrum drugs

Results were best when the abscess was excised Aspiration with or without drainage was commonly used The mortality figures were 62% in patients with abscesses secondary to lung suppuration 50% in those with abscesses secondary to mastoid infection and 17% in those with abscesses secondary to sinus infection

► [Paucity of systemic signs of infection is not uncommon in brain abscess and this makes differentiation from tumor difficult —Ed ]

**Cavernous Sinus Thrombophlebitis** is easily diagnosed according to P J Taylor[1] (St Thomas Hosp London) Patients present with chemosis and exophthalmos first of one eye then the other associated with profound pyemia The rapidity of progression is remarkable—death regularly follows in 6 48 hours after the second eye becomes involved Blood cultures are usually positive although the cerebrospinal fluid may be sterile

In 98 cases reviewed the original infections were furuncles of the face 53 (nose 25 lip 9 forehead 7 eyebrow 5 cheek 4 chin 3) ear infections 14 sinusitis 15 dental sepsis 8 sties 3 tonsillitis 3 erysipelas 1 facial injuries 1 and unknown 2 Staphylococcus aureus was isolated in 92% The incidence of penicillin resistant staphylococci is rising

In treating acute cavernous sinus thrombophlebitis while awaiting the results of culture and sensitivity tests penicillin therapy is not enough A broad spectrum antibiotic should also be given as soon as specimens have been taken for cul

(1) Brit J Ophth 41 2 8 37 Ap 1 195

ture There is no agreement on the value of anticoagulant drugs but the natural history of the condition with progressive thrombophlebitis suggests that prevention of further clotting might be valuable

The mechanism of the ophthalmoplegia usually found in one or both eyes at the height of the illness which may only partially resolve is yet unknown It may be due to involvement of the nerves within the cavernous sinus The 3d nerve is oftenest implicated 6th nerve palsies may occur and neuralgic pain may appear in the distribution of the ophthalmic division of the 5th nerve Of 60 patients who recovered only 1 was blind in both eyes and 3 were blind in one eye

The author reports on 2 patients in whom infection followed development of a sty 1 died

CASE 1 —Woman 24 had sty on lower lid of right eye The next day the eye was swollen and she had a headache On the 3d day the eye was extremely swollen and she felt ill On the 4th day the left eye began to swell and an hour later she was drowsy and disoriented On hospitalization she was comatose with marked meningism temperature of 104 8 F and severe bilateral proptosis and chemosis with edema extending across the upper part of the face The cerebrospinal fluid under high pressure contained 4 000 cells/cu mm but was sterile on culture The white blood cell count was 14 100 A right conjunctival swab grew Staph aureus The same organism was cultured from the blood

Immediate treatment consisted of 1 Gm streptomycin twice daily for 7 days and 1 Gm daily for another 7 days 1 000 000 units of penicillin every 2 hours for 14 days and 15 000 units of heparin subcutaneously every 12 hours for 14 days Erythromycin was started when the organism was identified and was continued for 24 days Local treatment to both eyes consisted of epinephrine solution and chlortetracycline cream

The temperature became normal on the 17th day and full consciousness was regained on the 20th day Primary optic atrophy remained in the left fundus with complete loss of sight Visual acuity in the right eye was 6/12

CASE 2 —Girl aged 2 weeks had a bad eye for a week and then suddenly became comatose She had proptosis and chemosis and a discharging sty The cerebrospinal fluid contained 210 cells/cu mm but was sterile A blood culture grew coagulase positive Staph aureus She was treated with streptomycin sulfadiazine penicillin and oxytetracycline Epileptic seizures followed and she died 2 days later

**Brachial Plexus Paralysis Following Administration of Tetanus Antitoxin** is reported in 3 cases by L Terrell Tyler I W Kaplan and Richard W Levy[2] (New Orleans) It is not generally known that serious neurologic complication can

(2) A J S g 95 668 678 Ap 1 1958

occur after injections of horse serum Signs and symptoms of neuritis usually appear at onset or at the height of serum sickness but may occur without other signs of serum disease Peripheral nerves usually are involved and in most instances such involvement is localized to the 5th and 6th cervical nerves in the brachial plexus The cause of serum neuritis and the reason why it is most commonly localized in the cervico brachial plexus are unknown The symptoms of brachial plexus neuritis usually occur within a few hours after onset of urticaria itching and polyarthritis with acute onset of severe neuritic pains in the neck shoulder and arm requiring large doses of opiates for relief Within a few hours flaccid paralysis of the muscles supplied by these nerves occurs Nerve involvement may be bilateral and symptoms may occur in the upper extremities The extremity affected is unrelated to the injection site of the antitoxin The paralysis gradually reaches a peak in 1 4 days The nerves involved in order of frequency are the axillary supracapsular and long thoracic The earliest subjective sign is inability to abduct the arm caused by involvement of the nerve supply to the shoulder cuff and deltoid muscles innervated by the axillary and suprascapular nerves Early treatment is symptomatic and supportive with complete rest of the extremity by abduction splint local heat analgesics and opiates As soon as the acute hyperesthesia subsides physical therapy should be started including electric stimulation and muscle re education About 80% of patients recover within 6 months but 20% have residual muscle weakness and atrophy

**Brucellosis in Egypt Review of Experience with 228 Patients** in the past 6 years is presented by W C E Pfischner Jr K G Ishak E M Neptune Jr S M Fox III Zoheir Farid and Gamal Nor El Din[3] (Cairo) These patients were selected from those who had a history suggestive of brucellosis and a brucella agglutination titer above 1 160 The brucellosis occurred in 219 males and 9 females aged 9 70 The actual sex incidence could not be studied because only a limited number of females were admitted due to the lack of convenient facilities for female patients Of the 228 105 were tradesmen 61 farmers and 24 laborers Most had daily intimate contact with animals

Most patients had weakness None had genitourinary com

(3) Am J Med 2 915 9 9 J e 1957

plaints The presenting symptoms are shown in Figure 11 Fever was present in 98% hepatomegaly was noted in more than half and splenomegaly in 70% Because of the high incidence of parasitic and protozoal intestinal infestations the role of brucellosis in the etiology of the hepatosplenomegaly could not be determined Musculoskeletal pain was noted in

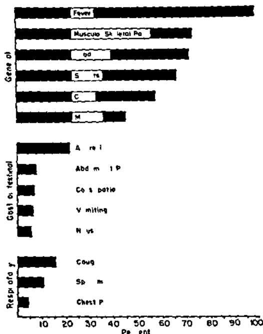



Fig 11—I d f mpl t t on adm (Court y of Pfisch W C F J t al Am J M d 2 915 929 Ju 1957 )

72% but only 3 had any objective evidence of joint involvement

All patients had positive cultures for Brucella melitensis Marrow cultures were taken from 50 patients but the blood culture was the better method of diagnosis

With single antibiotic therapy such as chlortetracycline oxytetracycline and chloramphenicol the relapse rate approached 50% With combined antibiotic therapy of oxytetracycline and streptomycin this rate was reduced to 14%

Differential diagno is includes paratyphoid and typhoid

fever pulmonary tuberculosis rheumatic fever rheumatoid and hypertrophic arthritis malaria subacute bacterial endocarditis Hodgkin s disease febrile malignancies and lupus erythematosus Parathyroid and typhoid fever may be difficult to differentiate clinically because they also show variable onset headache malaise leukopenia and splenomegaly The diagnosis of tuberculosis depends on identification of tubercle bacilli by smear and/or culture and radiographic evidence of lesions Objective joint involvement in rheumatoid arthritis is the most useful differentiating point in this disease

The illness lasted 3 months or less in 88% of the patients This agrees with the findings of others The white blood cell count was normal in most patients In only 10% was it elevated 17% had leukopenia Incidence of complications such as osteomyelitis endocarditis hepatitis encephalitis meningitis or pneumonitis was low After institution of specific therapy the temperature usually returned to normal within 5 days and the general condition improved

**Clinical Studies on Chloramphenicol in Treatment of Typhoid Fever** Typhoid fever is common in Karachi India with a season lasting from March to October Many factors are responsible for this wide prevalence including sudden influx of refugees rapid increase in population overcrowding lack of sanitation improper storage and supply of milk fly breeding during the summer dirty ice cream and sweet meat sellers and inadequate inoculation against typhoid A M Kassim[4] (Dow Med College) evaluated the benefits of treatment with chloramphenicol in 114 patients of whom 10% were under age 32 As there were no facilities for bacteriologic examination of blood stool or urine clinical criteria were rigid

Clinical diagnosis was based on a history of continuous pyrexia for 6-10 days coated furred tongue constipation doughy feel to the abdomen tenderness in the right iliac fossa palpable soft spleen and leukopenia Malaria was excluded by history and by thick smear examination for parasites A 4 hourly temperature chart revealed typical temperature curve The Widal reaction was invariably positive in titers of 1 100 1 400

Once the diagnosis was established half the patients received chloramphenicol Adults received 1 5 Gm initially and

(4) M d cu 13 253 259 March 1957

0 25 Gm every 2 hours until the temperature became normal then 0 25 Gm every 3 hours for 24 hours then every 4 hours for 48 hours Children received 0 5 1 Gm initially 0.25 Gm every 4 hours until the temperature was normal then 0.25 Gm every 8 hours for 48 hours The rest of the patients received conservative treatment liquid diet consisting of whey albumin water and citrated milk and 150 mg vitamin C daily

Average number of days of fever after start of chloramphenicol treatment was 4 08 Average total dosage was 13 Gm Of the 57 patients treated with the drug 7 died Those who died had received an average of 9 6 Gm and fever had been present for 17 days before death Among the 57 controls there also were 7 deaths Mortality thus appears to be unaffected by chloramphenicol but this drug was reserved only for patient with far advanced disease perforation had actually occurred in 2 Two had hemorrhage after the fever subsided on chloramphenicol therapy and in 1 perforation occurred during therapy The drug does not prevent hemorrhage or perforation Four patients had unduly low temperature 95 F with cold sweats thready pulse and collapse on the 3d day of chloramphenicol treatment Twelve of 50 patients treated with the drug relapsed an average of 15 days after treatment was stopped

The outstanding effect of chloramphenicol was reduction of the number of days of fever The entire course of fever was 14 8 days in those treated with this drug compared with 26 8 days in those treated conservatively

► [As the author points out the failure of chloramphenicol therapy to reduce the death rate may be due to the fact that the drug was given to the more severely ill patients Certainly there seems to be a clear difference between the two groups in duration of fever —Ed ]

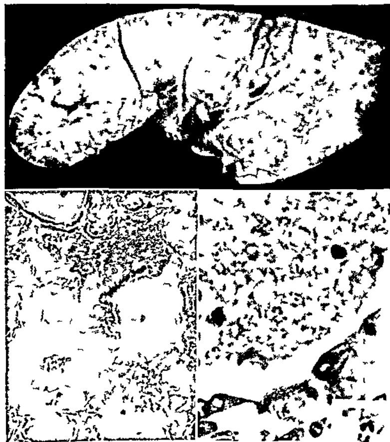
**Pneumocystis Pneumonia** This disease a pulmonary condition of infants previously known only on the European continent and caused by *Pneumocystis carinii* has evoked little comment in English medical journals R D K Reye and R E J ten Seldam[5] (Univ of Sydney) report 2 cases

Girl became ill at age 2 with severe coryza abundant nasal discharge and cough and weight loss to 28 lb by age 2½ Physical examination and extensive laboratory tests were negative except for ill-defined consolidations 1 2 mm in diameter scattered through the lungs She died after 6 months of gradually increasing dyspnea and cyanosis At autopsy the cut surface of the lung was a uniform light

(5) J P h & B et 7 4 1-458 Oct be 1956

grav flecked with small widely separated yellow foci (Fig 12) The alveoli ducts and bronchioles were filled with granular material staining light pink with hematoxylin and eosin (Fig 13)

With hematoxylin eosin the actual parasites inside their empty capsules are difficult to find Giemsa stain (Fig 14) or PAS staining however clearly differentiates the out



F g 1 (t p) —C t f f l g b w g l d t
F g 13 (bott m l ft) —Al eol l col d t a d b on h l fill d w th g l m t l w th d k r pl q H m t l e j t f om ×125
F g 14 (bottom r ght) —P ra t f l f t g l 7 m th app d r l g t d n d pt lly mpty p l O lly y t d l pm t l tag ( po gon ) occu w th 4 8 p ra t bod d l t h w w th 4 h bod s. G m ed d f om ×960 t d d f om ×19 0
(C rt f R R D F d t n S l l m R E J J P th & B t 72 451 458 Oct ber 19 6 )

er membrane and some of the acid mucopolysaccharide material in the clear swollen mucoprotein capsule

The parasitic origin of the honeycomb like material in the alveoli was first described in 1952 Differences of opinion exist as to the correct classification of the parasites and interpretation of their developmental stages Vanek and Jirovec considered them to be protozoa belonging to the order Haplosporidia No suitable test animal has yet been found and the parasites have not been cultured The mode of transmission is obscure The disease occurs in small epidemics in nurseries and hospital wards suggesting the possibility of droplet infection from immune perhaps adult carriers The disease is widespread Incidence is highest on the European continent but it varies in different countries The disease is common in Switzerland Austria Czechoslovakia East Germany Poland and Finland but apparently relatively rare elsewhere It is almost restricted to infants under age 1 mainly in the group aged 14 days to 6 months Both sexes are affected equally Those affected are mostly premature or poorly developed full term infants The disease is resistant to all known antibiotics The parasites have not been demonstrated in organs other than the lungs though they have been found in the alveolar walls

The peculiar age distribution of the disease leads to the supposition that lowered constitutional resistance must be present before the infection can become established

► [This disease is already well known in certain parts of the world notably in central Europe A few cases have been recognized on this continent and doubtless the rate of recognition here will increase —Ed ]

**Clinical Observations and Epidemiology of Human Ornithosis Transmitted by Pigeons** According to G Kemmerer H G Haussmann G Schoop and E Kauker[6] (Univ of Frankfurt) at least 62 different kinds of birds from 9 species can transmit ornithosis to man including sea gulls procellariae sparrows orioles pheasants pigeons chickens turkeys and ducks In Germany the ornithosis virus has been widely distributed in man through contact with these birds More human cases have been transmitted by pigeons than is realized In a serial examination of pigeon breeders in Northwest Germany complement fixation antibodies were found in the blood of 50% though none had suspected he disease The possibility of ornithosis should be considered in all un

(6) G m M Month 2 7 9 J ary 1957

gray flecked with small widely separated yellow foci (Fig 12) The alveoli ducts and bronchioles were filled with granular material staining light pink with hematoxylin and eosin (Fig 13)

With hematoxylin eosin the actual parasites inside their empty capsules are difficult to find Giemsa stain (Fig 14) or PAS staining however clearly differentiates the out



F g 1 (t p) —Cut s f f l g h w g on l d t n
F g 13 (bott m l ft) —Al eol l eol d t d b on h l fill l w th g l mat r l w th d k r pl q H m t l d e l f m 125
F g 14 (bottom right) P ra t f m l f t g l 7 m th pp ou d elo g ted le opt lly mpty p l O ca on lly y t d l pm t l t g ( p gon ) occ w th 4 8 p t bod d I t hows w th 4 a ch bod G m ed l f om ×960 set d d f m ×19 0
(C t y f Rey R D K nd ten S ldam R E J J P th & B t 2 451 458 Oct be 1956 )

on the right side a temperature of 102 8 F signs of consolidation of the right lower lobe and red jelly sputum X ray confirmed a homogeneous shadow in the right middle and lower zones The white blood cell count was 5 950 The psittacosis lymphogranuloma titers did not rise the streptococcus M G agglutination titer was low An intradermal injection of 0 1 ml cat scratch antigen produced an erythema and induration after 48 hours considered positive She was given penicillin and tetracycline and gradually improved The enlarged lymph nodes in the left arm steadily regressed

Complicating pneumonia has not been described previously in cat scratch disease In this case other possible causes such as pneumococcus psittacosis influenza Q fever or virus were excluded by bacteriologic and serologic tests The clinical findings history and positive skin test to cat scratch antigen suggest that the pneumonia was a complication of cat scratch disease

► [Maybe —Ed ]

**Salmonella Osteomyelitis in Patients with Sickle Cell Anemia** Isolated case reports of such an association have appeared since 1925 E W Hook C G Campbell H S Weens and G R Cooper[8] (Emory Univ ) report 4 cases of salmonella infection encountered in 36 consecutive cases of sickle cell anemia proved by hemoglobin electrophoresis Salmonella infections in patients with sickle cell anemia probably are more than just coincidence

One boy aged 15 months had a Salmonella paratyphi B infection in the radius which recurred 2 years after the initial episode Salmonella typhimurium infection was found in the humerus of a boy aged 3 and in the humerus femur and tibia of a man aged 23 Another man aged 23 had S cholerae suis bacteremia but no osteomyelitis

Thirty three cases of sickle cell anemia and salmonella infection have thus far been reported with a ratio of 3 1 in men Salmonella paratyphi B and S typhimurium accounted for two thirds of the infections Osteomyelitis was present in 31 of the 33 infections and developed at multiple foci in two thirds of them Two patients had salmonella bacteremia without apparent bone localization

Recognition of pyogenic osteomyelitis in patients with sickle cell anemia may be difficult because fever pain swelling in the extremities and leukocytosis occur in both diseases In several cases osteomyelitis was first recognized when a subperiosteal abscess drained spontaneously

(8) New Engl J Med. 257 403 407 Aug 29 1957

solved febrile disease or atypical pneumonia Ornithosis may be as serious as psittacosis as shown in the following cases

CASE 1—Man 35 had a febrile (102 2 F) illness with malaise headache vertigo and irritative coughing The family doctor made a diagnosis of pneumonia and administered various penicillin preparations Fluoroscopy on the 11th day showed an extensive infiltrative process predominant at the base of the right upper lobe and apex of the right lower lobe Bilateral basal atelectasis and a hairlike interlobar line were seen in the right middle lobe The white blood cell count was 5 000 Treatment was symptomatic and supportive because the etiology of the virus pneumonia was not clear After intensive and repeated questioning the patient admitted that he had taken care of pigeons for 6 months Serologic tests confirmed diagnosis of ornithosis On the 27th day the complement fixation titer was 1 1280++++ it was the same on the 38th day

Clinical course was dominated by severe cardiovascular involvement Tachycardia precordial stabbing pains dyspnea weakness and dizziness were prominent with severe frontal headaches painful cough and profuse perspiration The temperature became normal on the 15th day before the diagnosis was made From the 4th week the percussive dulness bronchial breathing and rales disappeared Eight weeks after onset the patient still had precordial pain dizziness and profuse perspiration and the ECG still showed slight changes

CASE 2—Man 60 had a febrile illness (104 F) diagnosed as pneumonia and treated with penicillin On the 10th day x rays showed a poorly defined apple sized shadow in the left lower lung lobe The patient denied any contact with birds but on the 13th day of illness an ornithosis titer of 1 160+++ was obtained by complement fixation by the 19th day it had dropped to 1 80+++ and remained at this level until the 35th day After repeated questioning the patient admitted he had looked after a friend s pigeons 2 weeks before onset of illness

The 1st patient kept 8 pigeons all of which were shown serologically to be infected Of 42 pigeons in the friend s flock cared for by the 2d patient 16 showed serologic evidence of ornithosis None of the birds had clinical symptoms of the disease Diagnosis was complicated by the patients denial that they were keeping pigeons they feared losing the birds once public health organizations had been informed

**Cat Scratch Disease with Pneumonia** A case is reported by G C Sheldon and Hugh Smellie[7] (King s College Hosp London)

Woman 46 worked in a household in which there was an aging cat In July she noted a small cyst on the palm of the left hand In September a slightly tender swelling appeared at the left elbow which was an enlarged epitrochlear lymph node An enlarged left axillary node was also found Two weeks later he had pleuritic pain

(7) Brit M J 2 446 447 Aug 24 1957

erysipelas which has cooled off The color is pathognomonic

The thin skin on the dorsum of the hand and fingers is commonly affected It spreads by continuity traveling up one side of the finger and down the next The fingers become stiff and swollen and full range of motion is lost It is uncommon for the spread to continue above the wrist crease Streaks of lymphangitis may be seen on the forearm with enlarged regional nodes The patient is seldom really ill Untreated the infection runs its own course and resolves completely in 10 days to 3 weeks

Its epidemiology is interesting The disease is largely occupational often occurring in butchers handling pork mutton and beef among slaughtermen workers handling cattle bones to make buttons those who work with pelts hides tallow and greases fertilizers or lard and even bakers The disease can follow an injury from a chicken bone It is common in fishing communities

The organism Erysipelothrix rhusiopathiae must be ubiquitous It is found in all putrefying nitrogenous material and is carried by houseflies It shows a seasonal incidence with a noticeable rise in the warm summer months—May to September in the northern hemisphere

Differential diagnosis includes erysipelas and septic arthritis Bacteriologic confirmation is seldom necessary although the organism can usually be recovered from incubating a slice of skin in glucose broth A course of penicillin will shorten an attack and decrease discomfort

**Rubella Arthritis Report of Cases Studied by Latex Tests** An interesting self limited polyarthritis often has been described in foreign literature as following rubella Robert E Johnson (Framingham Mass) and Arthur P Hall[1] (Boston) studied 10 patients who were thus affected All were young women Joint symptoms began shortly after the rash appeared and in each the fingers were involved first Many expressed concern that their rings would have to be cut off Small and medium joints were affected Tenderness was pronounced but none reported redness Symptoms subsided in each within 10 days In some secondary rise in temperature to 102 or 103 F occurred with onset of joint pains

The latex fixation test a variation of the sheep cell agglutination test for the so called rheumatoid factor in the serums

(1) New England J Med 258 743 745 Apr 10 1958

The most effective treatment of salmonella osteomyelitis appears to be chloramphenicol combined with surgical drainage Response is usually not dramatic Chloramphenicol is not bactericidal Drug sensitive organisms can persist in tissues for months even with prolonged therapy Activation of organisms which have persisted in the tissues may be responsible for recurrent osteomyelitis months or years after apparent healing of a previous infection

Several factors may cause the increased occurrence of salmonella osteomyelitis in patients with sickle cell anemia Capillary thromboses in the gastrointestinal tract can be compared with the effects of gastrectomy or gastroenterostomy in predisposing to salmonella infections debility and auto splenectomy may also decrease resistance to invasion The organisms may localize in areas of ischemia and necrosis resulting from the sickling process in a manner analogous to their localization in hematomas and neoplasms Ischemia of the bone marrow may also lower local resistance and permit growth of dormant organisms This might explain the observation that sickle cell crisis often precedes the symptoms of osteomyelitis

Erysipeloid is reviewed by Maurice Ewing[9] (Univ of Melbourne) This disease was first described by Baker in 1873 It usually follows a trivial injury and because it spreads by direct continuity to adjoining skin in a peripheral direction was first called erythema serpens About 10 years later it was first clearly established as a clinical entity and called erysipeloid and since has been given the eponymous title erysipeloid of Rosenbach after the man who delineated the disease

First the disease appears to be a streptococcic infection of the skin of the hand The patients never look ill The course is mild but seems to relapse mysteriously always resolving without pus formation or residua

Erysipeloid characteristically affects the hands with few exceptions A few days to 2 weeks after a trivial injury the surrounding skin becomes swollen and rises 3-4 mm The surface remains smooth and unbroken without papules or vesicles and resembles the effect of an intracutaneous injection The skin color is purplish red livid red violet red or dusky red but never the vivid red of erysipelas It looks like

(9) M J A t alia 1 449-452 Ap 6 1957

erysipelas which has cooled off The color is pathognomonic

The thin skin on the dorsum of the hand and fingers is commonly affected It spreads by continuity traveling up one side of the finger and down the next The fingers become stiff and swollen and full range of motion is lost It is uncommon for the spread to continue above the wrist crease Streaks of lymphangitis may be seen on the forearm with enlarged regional nodes The patient is seldom really ill Untreated the infection runs its own course and resolves completely in 10 days to 3 weeks

Its epidemiology is interesting The disease is largely occupational often occurring in butchers handling pork mutton and beef among slaughtermen workers handling cattle bones to make buttons those who work with pelts hides tallow and greases fertilizers or lard and even bakers The disease can follow an injury from a chicken bone It is common in fishing communities

The organism Erysipelothrix rhusiopathiae must be ubiquitous It is found in all putrefying nitrogenous material and is carried by houseflies It shows a seasonal incidence with a noticeable rise in the warm summer months—May to September in the northern hemisphere

Differential diagnosis includes erysipelas and septic arthritis Bacteriologic confirmation is seldom necessary although the organism can usually be recovered from incubating a slice of skin in glucose broth A course of penicillin will shorten an attack and decrease discomfort

**Rubella Arthritis Report of Cases Studied by Latex Tests** An interesting self limited polyarthritis often has been described in foreign literature as following rubella Robert E Johnson (Framingham Mass ) and Arthur P Hall[1] (Boston) studied 10 patients who were thus affected All were young women Joint symptoms began shortly after the rash appeared and in each the fingers were involved first Many expressed concern that their rings would have to be cut off Small and medium joints were affected Tenderness was pronounced but none reported redness Symptoms subsided in each within 10 days In some secondary rise in temperature to 102 or 103 F occurred with onset of joint pains

The latex fixation test a variation of the sheep cell agglutination test for the so called rheumatoid factor in the serums

(1) New E gland J M d 58 743 745 Ap 10 1958

The most effective treatment of salmonella osteomyelitis appears to be chloramphenicol combined with surgical drainage Response is usually not dramatic Chloramphenicol is not bactericidal Drug sensitive organisms can persist in tissues for months even with prolonged therapy Activation of organisms which have persisted in the tissues may be responsible for recurrent osteomyelitis months or years after apparent healing of a previous infection

Several factors may cause the increased occurrence of salmonella osteomyelitis in patients with sickle cell anemia Capillary thromboses in the gastrointestinal tract can be compared with the effects of gastrectomy or gastroenterostomy in predisposing to salmonella infections debility and auto splenectomy may also decrease resistance to invasion The organisms may localize in areas of ischemia and necrosis resulting from the sickling process in a manner analogous to their localization in hematomas and neoplasms Ischemia of the bone marrow may also lower local resistance and permit growth of dormant organisms This might explain the observation that sickle cell crisis often precedes the symptoms of osteomyelitis

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(9) M J A tralia 1 449-45 Ap 6 1957

lar tissue itself and is excreted in the saliva thus completing the cycle Viremia apparently is not part of the usual pathogenesis of rabies

Rabies prophylaxis is unique since it is the only instance in medical practice in which active immunity is attempted after exposure This is a rational procedure only because of the relatively long incubation period of 10 days to 1 year but usually within 20 90 days after exposure

A competent veterinarian should evaluate the animal Not all rabid animals have the furious type of rabies characterized by the mouth frothing blindly biting excited mad dog Many have the dumb or paralytic type Any dog that has a sudden change in disposition should be suspected

The first consideration in man is treatment of the bite wound itself Free bleeding should be encouraged without trauma followed by thorough mechanical cleansing using adequate water with soap or detergents Fuming nitric acid no longer is considered specific treatment

Antirabies vaccine is the crudest of all biologic products for parenteral use in man It consists of a whole unpurified heavy suspension of the brains of laboratory animals infected with rabies virus Most vaccine is the attenuated or killed virus type Relatively large and frequent doses are given because rapid immunity is important For ordinary exposure without severe trauma to any part of the body other than a bite on the head and neck a course of 14 daily injections is usually recommended For bites on the head or neck or if trauma is severe 21 daily doses are given

Practically all treated individuals develop some sensitivity to the material during immunization By the time of the 7th daily dose large painful indurated swellings appear not only at the site of the most recent inoculation but often at all previous sites This is not serious and the vaccine should not be discontinued The most severe complication is organ specific sensitivity Postvaccinal paralysis or iso allergic encephalitis appears to be due to hypersensitivity to the brain tissue in the vaccine leading to a demyelinating destruction of the patient s central nervous system

The only way to avoid this dangerous complication is the discriminate use of the vaccine It should be administered only if definitely indicated ACTH or cortisone and perhaps antihistaminics might be useful

of patients with rheumatoid arthritis was used Latex particles are substituted for the more complex and variable sized sheep erythrocytes This test was positive in 9 (90%) of 10 patients with rubella and polyarthritis and in 2 (28 6%) of 7 with rubella without arthritis

It is possible that rheumatoid arthritis is caused by a viral infection in a susceptible host The cases of rubella arthritis may afford an opportunity to isolate a causative virus for rheumatoid arthritis because rubella occurs epidemically at predictable times Under these circumstances, the nose throat blood feces and joint fluid specimens could be obtained in an early phase of the illness the period most likely to yield a specific agent

► [This short self limited polyarthritis which sometimes complicates rubella does not seem to me to bear much resemblance to rheumatoid arthritis and I see little justification for speculation that the positive serologic reaction with latex particles raises hope of finding a virus causally related to rheumatoid arthritis —Ed ]

## VACCINES FOR VIRUS DISEASES

**Rabies Prophylaxis in Man** is reviewed by Karl Habel[2] (Nat l Inst of Health) The number of rabid animals reported annually in the United States varies from 6 000 to 10 000 but the actual number is estimated to be about three times this amount *Only 10 20 human deaths are ascribed to* rabies yet as many as 50 000 persons receive antirabies prophylaxis yearly

The presence of rabies in other animals in this country is noteworthy Rabid foxes and skunks continue to infect dogs farm animals and man In 1953 it was first demonstrated in bats in Florida which is now recognized as an important reservoir The bats involved are the common fruit and insect eating species but they rarely attack man

Experimental inoculation of rabies street virus into mice shows the virus is demonstrable for 4 days at the inoculation site By the 2d day it is already present in the sciatic nerve and by the 4th day it is in the central nervous system There it multiplies and spreads along peripheral nerves including those which supply the salivary glands When it reaches the salivary glands it again multiplies apparently in the glandu

(2) P Health Rep 72 1936 May 1957

viruses are a principal cause of acute respiratory illness among newly recruited military personnel in the general category of febrile catarrhs and the specific syndromes of undifferentiated acute respiratory disease (ARD) nonstreptococcic exudative pharyngitis atypical pneumonia unassociated with cold agglutinins and pharyngoconjunctival fever Extensive studies in military camps have shown that the adenoviruses cause hospitalization of roughly 10% of the entire basic trainee component of a training post during the year and during winter months up to 90% of all hospital admissions

Adaptation of adenoviruses to growth in tissue cultures of monkey kidney made possible the production of a vaccine, It is a bivalent material containing types 4 and 7 adenovirus, the two types which account for most cases in military recruits Extensive field trials have proved the vaccine to be highly effective in preventing illness caused by these two types The bivalent vaccine effected a 90 98% reduction in adenovirus cases the trivalent vaccine an 83% reduction

This vaccine clearly promises to eradicate adenovirus caused respiratory disease as an important medical problem in the Armed Forces

In striking contrast to their behavior in military recruit populations the adenoviruses appear to be responsible for only a fraction of the respiratory illnesses among adult civilians Studies among families university students university employees and selected cases of acute respiratory illness from hospitals or private practice have shown low attack rates for respiratory illness caused by adenovirus Until definitive evidence is obtained of need for such a vaccine in a civilian population general use of the vaccine is not warranted Whether an adenovirus vaccine is needed for children what types to be included in the vaccine and how effective such a vaccine would be are important problems for future research

► [A very important development for military medicine which is preventing a major cause of disability in recruits The mystery is why this kind of respiratory illness is found so much less often in civilian populations —Ed ]

**Allergy (Asthma) to Monkey Protein in Poliomyelitis Vaccine** is reported by Seymour B Crepea[4] (Univ of Wisconsin) The Salk vaccine is being used on a large scale It is prepared by growing the virus in monkey kidney cells in an

(4) J All gy 8 262 63 M y 1957

Although rabies vaccine has been used for 70 years there are still questions raised as to its efficacy in the post exposure prophylaxis of the disease Pasteur s original experiments involved small numbers of animals and statistics on human treatment are difficult to evaluate because the degree of exposure is variable and in most instances rabies is not proved in the biting animal In well designed and controlled experiments in animals no protection resulted when exposure to street rabies virus was followed by a course of vaccine However when quantitative aspects of experiments are well balanced protection though of low level can be demonstrated

Theoretically rabies is the ideal disease for passive immunization with immune serum The exact minute of exposure is known as is the exact individual responsible for the exposure and the exact location on the body where the infection was introduced Antirabies serum has proved extremely effective if given in 2 doses even in the severe bites about the head and neck which usually carry a mortality rate of 40 50%

A single or double dose of antiserum given at the start of treatment followed by 14 21 daily doses of rabies vaccine gives a significant level of circulating antibodies continuously from the 1st day through as long as 50 days The early antibody is passive after the 10th day antibody is developed because of the vaccine Antiserum plus vaccine provides the best prophylaxis of rabies in man and the combination should always be used in cases of severe exposure The antirabies serum currently available in the United States is a partially purified and concentrated horse serum product Dosage is 0 5 ml /kg body weight In severe exposures a second dose is given 4 5 days later

► [Note that rabies antiserum is now available Although tried in comparatively few human beings the evidence for its effectiveness is convincing —Ed ]

**Efficacy of and Indications for Use of Adenovirus Vaccine** are reviewed by Maurice R Hilleman[3] (Walter Reed Inst of Research) The virus caused acute respiratory illnesses of man are one of the last great frontiers in infectious disease The discovery in 1953 of the adenoviruses was the most significant advance in knowledge of acute respiratory illnesses since the discovery of human influenza virus in 1933 These

(3) Am. J P b H alth 48 153 158 F bru ry 1958.

between 1946 and 1953 There were 111 such cases The number diagnosed appeared to be increasing during the period of the survey particularly among the elderly This may well represent a true increase in incidence

A useful classification was the presence or absence of pulmonary involvement A group of patients was obtained characterized by the presence in each of at least three (usually more) of the following a characteristic respiratory illness preceding the onset of systemic polyarteritis high blood eosinophilia (1 500/cu mm or more) numerous eosinophils in acute polyarteritic lesions pulmonary polyarteritis granulomatous polyarteritis giant cells in polyarteritic lesions and the presence in viscera of necrotizing or granulomatous lesions not demonstrably related to arteries The condition in this group which comprised one third of the cases was called polyarteritis nodosa with lung involvement From a study of previous reports it appears that similar cases have been given a variety of names including Loffler s syndrome Harkavy s syndrome Wegener s granuloma etc The reasons for adding another name to this list are (1) a newly defined group is being described and (2) previously suggested terms are too cumbersome for general use The term polyarteritis nodosa with lung involvement stresses the chief criterion of the syndrome without implying any particular etiology It is not clear whether the two syndromes with and without lung involvement are distinct diseases or merely variants However it is the most valid classification thus far proposed and it is of practical value in clarifying the natural history of the disease

There were 66 patients (41 men) who had polyarteritis nodosa without lung involvement Of these 55 died and autopsies were obtained in 54 The age incidence showed a steady rise throughout life to a maximum in the 7th decade Onset most often was in winter months No correlation was noted with occupation or smoking habits A constitutional illness was prominent at some stage Slight to moderate eosinophilia was noted in 30% Coronary polyarteritis was present in 48% Pulmonary manifestations were all attributable to infections or heart failure The kidneys were involved in 79% and nearly all had proteinuria and microscopic hematuria Ten died of renal failure and a form of glomerulitis was present in 16

artificial nutrient substrate Virus removed from cultures carries small amounts of monkey tissue protein together with whatever protein was used as part of the nutrient substrate No previous case of reaction to the monkey protein has been reported

Boy 9 whose parents were Rh positive and whose father had asthma was being treated for an inhalant form of allergic rhinitis and asthma Since age 4 he had had severe conjunctivitis rhinitis and asthma on visiting various animal houses at the zoo especially the monkey house

A few hours after receiving 1 cc poliomyelitis vaccine asthma of moderate severity developed along with a stuffy nose The arm was not swollen The asthma lasted 1 day and subsided One month later a second dose of 1 cc vaccine induced asthma and rhinitis in a few hours which lasted for 3 days A scratch test with 1 10 dilution of poliomyelitis vaccine produced an immediate wheal and flare reaction A control test on a normal subject was negative

Presumably this child was highly allergic to monkeys because of the zoo exposures and the injection of poliomyelitis vaccine containing small amounts of monkey protein caused an allergic response 5 years later

This situation will probably occur only rarely but the possibility of similar reactions particularly with repeated injections of the vaccine must be borne in mind

► [This kind of reaction to polio vaccine has fortunately been extremely rare —Ed.]

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## COLLAGEN DISEASES

**Natural History of Polyarteritis** In 1952 the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council began a clinical trial of cortisone in polyarteritis nodosa Concurrent untreated controls were not justifiable and retrospective study was necessary Cases reported in the literature are unsuitable because they are a selected group and often inadequately followed up A new body of data had to be collected from an unselected and consecutive series of cases studied specially for this purpose Such a study presented an opportunity not only to learn the prognosis and duration of the disease but also to make a comprehensive survey of its natural history and pathology

Geoffrey A Rose[5] (London) surveyed all histologically proved cases of polyarteritis under care at 9 teaching centers

(5) Brit M J 2 1148 1152 No 16 1957

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Valid blood pressure readings were available in 55 of these cases In 15 hypertension developed during the course of the disease In 16 the blood pressure was raised at the initial measurement Hypertension in polyarteritis nodosa is in almost all cases a sequel of renal polyarteritis or glomerulitis but the pressure rises only during the healing or healed stages of the lesions Once initiated hypertension is progressive It terminated in the malignant phase in 11 patients

Evidence of gastrointestinal polyarteritis in 46 of the 66 patients (70%) was most common as localized pain Muscle pain and tenderness were frequent and 27% had arthritis The spleen was palpable in 8 and peripheral nerve lesions were present in 24 Eighteen had focal indurated skin lesions A correct clinical diagnosis was reached in 31 patients (47%) but was frequently delayed in 22 of these the diagnosis was proved by biopsy

Of the 66 patients 12 were treated with cortisone or corticotropin Of the other 54 51 died (one third within 3 months and two thirds within 6 months) 3 had full remission in 2 of whom the lesions appeared to be confined to the skin and joints The figures on prognosis of the disease are heavily weighted by cases that were first diagnosed at necropsy A true assessment of the prognosis of the untreated disease needs to be based on cases proved in life by biopsy during the precortisone era

The syndrome of polyarteritis nodosa with lung involvement was present in 32 (16 men) Loss of weight fever and tachycardia were prominent features Eosinophilia observed in 69% exceeded 1 500/cu mm at some stage in 50% but was often intermittent In 36% the highest count was 5 000/cu mm or more A respiratory illness occurred in all patients and in all but 1 it preceded the onset of systemic polyarteritis (usually by less than 1 year but occasionally by up to 7 years) This phase was associated with specific pulmonary lesions Clinically the main features were asthma pneumonia or chronic bronchitis The incidence of polyarteritis in other organs and accompanying clinical manifestation were similar to those seen in cases without lung involvement

The etiology of the disease remains obscure The most likely clue is the relation to preceding chronic and acute respiratory infections (especially those due to hemolytic streptococci) One of the chief problems is to distinguish whether

the significant association is with the infections or with their treatment The evidence favors incrimination of the infection itself

► [Because of the way in which this series of cases was brought together it represents an ideal source for analysis of the clinical features of polyarteritis The article should be looked on as a standard reference and the succeeding one by the same author discusses a major subdivision of the whole series —Ed ]

**Clinical Features of Polyarteritis Nodosa with Lung Involvement** These pulmonary manifestations are unfamiliar to most physicians and often lead to errors in diagnosis G A Rose[6] (St Mary s Hosp London) surveyed 111 proved cases of polyarteritis nodosa under care in 9 hospitals between 1946 and 1953 In only a third was there evidence of lung involvement The cases with lung involvement appeared in many respects to form a distinct group Lung lesions almost always preceded the appearance of polyarteritis in other organs and produced a characteristic respiratory illness often associated with eosinophilia After an interval of days to years evidence of polyarteritis appeared usually suddenly in other viscera and thereafter the course was rapidly progressive

The disease affects the sexes equally Incidence increases with age reaching a maximum in the 6th and 7th decades Radiologically the lungs are characterized by numerous small shadows of miliary or near miliary size that tend to be slightly larger and more irregular than the shadows of miliary tuberculosis Transient infiltrations may occur In patients with a pneumonic type of illness the lesions tend to be more extensive denser and more persistent They may be progressive but more often tend to resolve in one area only to appear in another The rates of growth and resolution tend to be faster than in tuberculosis but slower than in Loffler s syndrome The clinical manifestations of polyarteritis in systemic organs are identical with those that occur in patients without lung involvement

The diagnosis of polyarteritis nodosa should be considered whenever a patient with atypical lung disease develops unexplained lesions in other organs especially if eosinophilia or asthma is present Biopsy of skin lesions which are recent and not ulcerated is valuable in diagnosis Healed arterial lesions may be unrecognizable and ulceration and secondary

(6) Brit. J T be 51 113 122 April 1957

infection make it impossible to determine whether vascular changes are primary or secondary In the absence of suitable skin lesions blind muscle biopsy offers about a 50% chance of a positive result Since the initial respiratory phase often precedes the appearance of generalized disease especially in patients with asthma many patients must be receiving medical care without the true diagnosis being recognised

Differential diagnosis must include tuberculosis sarcoidosis cancer bronchial asthma parasitic infestations and simple chronic infections The commonest misinterpretation of radiologic findings is a diagnosis of tuberculosis Sarcoidosis like polyarteritis nodosa may produce pulmonary disease associated with a raised sedimentation rate high plasma globulin level and evidence of lesions in other organs Confusion has sometimes also arisen histologically between the granulomas of the two conditions

**Periarteritis Nodosa and Appendectomy** Three cases observed by H Cottier and W Vogt[7] (Univ of Bern) suggest the diagnostic value of appendectomy in patients with abdominal symptoms A fourth case in which death resulted from appendical perforation indicated that appendectomy may also have prophylactic value

*The first 3 patients (men aged 56 52 and 42)* had been ill 1½ 3 months Diagnosis was indefinite and appendectomy was performed on suspicion of appendicitis or appendical abscess In Case 3 unusual whitish nodules were noted in appendical and cecal serous membranes Minute nodules were also found histologically in the other 2 cases In all 3 only a fraction of the sections showed typical changes of periarteritis nodosa (35% in Case 1 15% in Case 2 and 30% in Case 3) The appendical lumen was retained in Cases 1 and 3 *in Case 2 there was a connective tissue obstruction* near the tip In all periarteritic changes involved prearterioles and often also medium sized vessels Their lumens were usually narrowed by connective tissue and partially organized thrombi The endothelial cells were often increased The intima was partly thinned but sometimes definitely thickened and rich in cells with swollen fibroblasts the media showed definite fibrinoid necrosis strewn with nuclear fragments (Fig 15) and here and there with threadlike fibrin The adventitia was *often greatly thickened* with vas

(7) Schweiz med Wchnschr 87 638 642 June 1 1957

cular granulation tissue or connective tissue rich in cells In all layers of the wall but usually thickest in the adventitia and media there was infiltration by neutrophils and eosinophils some plasma cells histiocytes and lymphocytes Elastic internal and external membranes were often destroyed



Fig 15 P arte t n append x (C se 3) Not hh n I nec os f med a nt m sl ght nd in adventit a heavy p l i r tio t fib l l. ts i fl mm t y infl at i all l y f arte l w ll esp l y d ent t He t x l n (Court y f Cott H a d V gt W S hw med Wchnschr 8 633 64 J e 1957 )

or broken and heaped up Small veins near periarteric lesions showed sparse inflammatory wall infiltrations but were otherwise intact

In Case 4 appendical lesions of periarteritis nodosa led to acute appendicitis perforation and death Autopsy also showed classic lesions of generalized periarteritis nodosa in the kidneys liver gallbladder and small intestine and diffuse fibrinopurulent peritonitis

Good response to Meticorten® treatment was obtained in Cases 1 and 3 the patients were symptom free 16 and 7 months respectively after operation In Case 2 immediate response to Ultracorten® was noted but treatment failed to halt progress of the disease Nine months after operation the patient had continuous abdominal pain and the general condition was poor

The authors emphasize the diagnostic value of finding

necrotizing arteritis in the appendix by systematic examination of serial sections With more careful microscopic study more cases of this type may be found The presence of typical lesions in the appendix indicates generalized periarteritis for which a fatal course can be predicted

**Incidence of Disseminated Lupus Erythematosus Follow up Studies Indicating Increased Frequency** This disease is no longer the medical curiosity and rarity it was not many years ago Perhaps this change is due to improved diagnostic technics but from a study of three 2 year periods 1938 39 1948 49 and 1954 55—Alvar Svanborg and Lennart Solvell[8] (Goteborg Sweden) conclude that the incidence has actually increased The 1938 39 period was chosen because it was before the advent of sulfonamide and antibiotic therapy and 1948 49 because these were the first years roentgenograms were available for follow up study

Three patients were treated during each of the first two periods but during 1954 55 the total treated was 18 In relation to the population in the area and the number of patients admitted during the respective periods the probability that the increase is statistically significant is at the 1% level

Diagnoses were based on the clinical picture Follow up was available on the earlier cases In none was diagnosis based on an atypical clinical picture with positive L E cell phenomenon Thus diagnostic criteria were the same in all three periods The cause of increased incidence is speculative since the cause of the disease is unknown If toxic or allergic or immunologic pathogenesis is accepted and the known increase in contact with sulfonamides antibiotics preservatives and dyes is considered possibly increased incidence of the disease is related to these substances The fact that this study was based on follow up of patients in which all were traced is the best argument for such a conclusion

► [The succeeding article from the same clinic provides a clue to the reason for the apparent increasing incidence of this disorder —Ed ]

**Lupus Erythematosus Disseminatus after Administration of Mesantoin® Report of Two Cases** is presented by Torsten Lindqvist[9] (Univ of Goteborg) It is still uncertain whether this syndrome has a common etiology or whether it should be considered a specific reaction to various noxious

(8) J A M A 165 11 6 1128 N 2 1957
(9) A t med sc d nav 158 131 138 1957

influences Apresoline® is known to produce symptoms in distinguishable from lupus erythematosus disseminatus which disappear when the drug is discontinued

CASE 1 —Woman 24 had episodic attacks of dizziness faintne s and inability to speak Mesantoin® 0 1 Gm twice daily provided some relief *One year later tender swollen nodules appeared on the* finger tips the joints became swollen and the skin scaled Six months later she had a severe headache stiff neck and fever Results of puncture were normal The following month the distal parts of all fingers were alternately atrophic and hyperkeratotic the interphalan geal joint of the right middle finger was fusiformly swollen She had severe muscular pain and weakness the tendon reflexes in the arms disappeared A severe stomatitis developed and white spots were found in the left eyeground Within a month she improved with a decrease in paresis and normal temperature attributable to treatment with ACTH Examination of the blood had revealed anemia and leukopenia but no L E cells The serum protein was reduced to 5 5 gm /100 ml but the globulins especially gamma globulin were *relatively and absolutely increased The urine* contained small amounts of protein

In this case diagnosis of lupus erythematosus dissemi natus seems established by the combination of symptoms from skin joints mucous membranes kidneys peripheral nerves retina blood picture and hyperglobulinemia and the favorable response to ACTH

CASE 2 —Girl 17 had convulsions at age 6 At age 13 after a severe status epilepticus she was given Mesantoin® One month later the temperature rose to 104 F and the cervical glands were swollen Thirteen months later she becam pale and thin and was hospitalized *Temperature again rose to 102 2 F* the white blood cell count was 5 200 and the *skin on the fingers and toes underwent a* strange alteration over the distal phalanges it was flushed infiltrated and scaling Many pea bean sized nodes appeared on the sides of her neck A rough systolic murmur was heard Movements of the shoulder elbow and wrists caused pain A butterfly shaped redness appeared on the cheek and nose Shortly after admission laboratory examina tion showed a normochromic anemia leukopenia and typical L E cells ACTH was given and symptoms di appeared within a few weeks The general condition improved rapidly

In both cases a typical picture of lupus erythematosus disseminatus developed after administration of Mesantoin® In Case 1 the first symptoms appeared after about 1 year of treatment and in Case 2 after a few weeks

In some cases of lupus erythematosus disseminatus re ported in the literature epilepsy has been regarded as an early symptom Perhaps this disease actually originated as a result of the treatment given for the epilepsy When treat

ing epilepsy with Mesantoin® slight symptoms of intolerance may be the initial signs of lupus Interruption of therapy is recommended If the more serious symptoms of lupus occur steroid therapy should be started

**Rheumatoid Arthritis and Systemic Lupus Erythematosus** Mary Bateman, J M Malins and M J Meynell[1] (Gen l Hosp Birmingham England) report 28 cases with features of chronic rheumatoid arthritis in which L E cells were demonstrated in the peripheral blood In each case the arthritis was typically rheumatoid involving the hands wrists elbows shoulders ankles and knees the jaw joints were affected in 15 and the hip in 6 In 22 the disease was advanced with ulnar deviation of the hands disorganization of the wrists and gross muscle wasting Only 3 patients had the classic erythema of butterfly distribution on the face All the patients had a positive L E cell test on at least two occasions and 23 had never received cortisone at the time the first positive result was obtained

The concept of systemic lupus erythematosus as a widespread systemic disease which does not always involve the skin has been greatly advanced by the discovery of the L E cell phenomenon and the widely held belief that it is specific for this disease only However positive tests have been reported in hemolytic anemia miliary tuberculosis rheumatoid arthritis chronic hepatitis pernicious anemia subacute glomerulonephritis and sensitivity to hydantoin penicillin and hydralazine In most of these case records there are clinical features suggesting systemic lupus erythematosus as a background to the presenting diagnosis

Rheumatoid arthritis is more than a disease of the joints and is more properly called rheumatoid disease Perhaps it is unnecessary to distinguish rheumatoid arthritis from systemic lupus erythematosus Are these cases of systemic lupus erythematosus with predominantly arthritic manifestations rheumatoid arthritis with coincidental systemic lupus erythematosus or rheumatoid arthritis with unusual antibody formation giving rise to false positive L E tests? It seems best to consider them as cases of systemic lupus erythematosus presenting as rheumatoid arthritis

► [This seems to me to be the soundest point of view The L E phenomenon has turned out to be remarkably specific —Ed ]

(1) Ann Rheumat D 17 114 118 March 1958

**Neuropathy in Rheumatoid Disease** is prevalent although the literature on the subject is scanty F Dudley Hart J R Golding and D H Mackenzie (Westminster Hosp London) report 11 cases In each the clinical significance of the neuropathy was obvious and in most was a prominent complaint often the major disability according to the patient All cases occurred in long standing advanced rheumatoid arthritis but not in periods of natural exacerbation or relapse In the 2 most severe cases the severe motor and sensory changes occurred within 2 weeks of abruptly stopping steroid therapy and in 2 other cases within 4 weeks of discontinuing steroid therapy Thus 4 cases appeared to be precipitated by steroid withdrawal

The sensory changes were symmetrical as compared with the frequent asymmetry of the neuropathy of polyarteritis nodosa If the feet only were affected the outer part showed more marked changes than the inner The disorder was unlike lupus erythematosus Other causes were looked for but no signs were present Development of neuropathy was not heralded or accompanied by fever or systemic upset or by any particular elevation of sedimentation rate or sudden alteration in the pattern of plasma proteins

The neuropathy appears to be due to arteritis which is part of the rheumatoid disease process It is a complication of rheumatoid arthritis It cannot be considered entirely a polyarteritic complication of steroid therapy because 5 of the patients had never had steroids The concept of diffuse arteritis as part of the rheumatoid disease best explains these cases Withdrawal of steroid therapy particularly if abrupt may precipitate more florid changes Demyelination is merely a feature of ischemic change and is a nonspecific finding

**Acute Rheumatic Fever in Children Comparison of Six Forms of Treatment in 200 Cases** is presented by R S Illingworth J Lorber K S Holt and John Rendle Short[3] (Univ of Sheffield) with statistical addendum by G H Jowett and Wendy M Gibson The study was controlled and compared salicylates bed rest alone and cortisone and various combinations of salicylates and cortisone

Duration of arthritis was shorter in cortisone than in salicylate groups and shorter in the salicylate than in the

(2) A Rh um t D 26 471 480 D embe 1957
(3) L et 2 653 659 O t 5 1957

no treatment group New rheumatic manifestations (nodules heart failure pericarditis chorea or arthritis) did not develop during treatment in cortisone groups—a course significantly different statistically from that in groups treated with salicylates

Groups treated with cortisone fared better than all other groups in respect to carditis More children receiving cortisone with salicylates lost organic systolic murmurs than did children receiving salicylates alone and more receiving cortisone lost the murmur than did those treated with salicylates Children fared better on cortisone with salicylates than on cortisone alone Significantly more children in cortisone groups lost all evidence of carditis when they were hospitalized for treatment less than 30 days after onset of rheumatic fever than did those hospitalized later Temperature fell more quickly in cortisone than in salicylate groups and more quickly in the salicylate than in the no treatment group

Cortisone with salicylates especially in high dosage was more effective than any other treatment though cortisone alone was more effective than salicylates alone

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## DISEASES OF UNCERTAIN ETIOLOGY

**Ardmore Disease** William L Wilson Charles D Williams Saul L Sanders and R P Warner[4] report the outbreak and subsequent course of a highly infectious epidemic disease at Ardmore Okla Air Force Base during the fall of 1955 It was characterized by upper respiratory infection prolonged malaise generalized adenopathy painful hepatosplenomegaly and pronounced tendency to relapse into a chronic smouldering illness of several months duration The clinical course superficially resembled that of infectious mononucleosis or infectious hepatitis with some aspects of epidemic pleurodynia Notable differentiating points were absence of jaundice and of atypical lymphocytes and consistently negative heterophil agglutinations

*The first* few cases were seen in late August By early September the incidence increased to alarming proportions

(4) A M A A h I t M d 100 943 950 D ember 1957

with as many as 10 new cases daily Initially some patients were treated as outpatients with restricted activity but when the seriousness was realized all were hospitalized Most of those initially treated at home were later hospitalized Despite rigid isolation technic and elaborate precautions 2 physicians 3 nurses and 9 of 15 corpsmen assigned contracted the disease within 2 weeks

The commonest complaint was pain mostly deep in the lower chest and accentuated by deep breathing or any jarring motion Others had pain in the upper abdomen accentuated by any jarring motion such as walking The next commonest complaint was sore throat Myalgia generalized or localized in the quadriceps or back headache nausea and vomiting were also present The liver was palpable in 92% The spleen was palpable and acutely tender on admission in 28% and later became palpable in 48% Neither pleural nor pericardial friction rubs were noted

Most patients were hospitalized 4 weeks and treated with bed rest and high protein high carbohydrate diet with supplemental vitamins Duration of hospitalization was 1 30 days in 13% 31 50 days in 21% 51 70 days in 27% 71 100 days in 8% 101 150 days in 8% and over 150 days in 24% Despite the many similarities to both infectious mononucleosis and infectious hepatitis this disease does not fit the diagnostic criteria for either Though hepatomegaly was marked liver function was not pronouncedly deranged nor was the histology abnormal The number of relapses was unusual for what appeared to be a benign disease and relapses were much more severe and of longer duration than the original disease process

► [A remarkable disease! Note that duration of hospital stay was more than 5 months in about one fourth of the cases There is a little resemblance to the outbreaks described in the succeeding three articles —Ed ]

Epidemic Neuromyasthenia Outbreak in Punta Gorda Florida in the spring of 1956 is reported by David C Poskanzer Donald A Henderson E Charles Kunkle Seymour S Kalter Walter B Clement and James O Bond[5] Clinically it was characterized by fatigue headache nuchal pain alterations in emotional status and mentation nausea and vomiting paresthesias aching muscular pain and prolonged relapsing course Similar epidemics have been described as Iceland disease benign myalgic encephalomye

(5) New England J Med 57 356-364 Aug 22 1957

litis Akureyri disease and epidemic vegetative neuritis Young and middle aged adults are affected, predominantly women Incidence is disproportionately high among medical and associated personnel

Of the 21 persons selected for detailed study 17 were women all were white and age range was 14-60 with median age of 30 Tension and depression usually were severe persistent and overt with terrifying dreams and episodes of crying without provocation Memory was defective primarily for recent events ability to calculate was impaired and there were transient periods of apparent mild confusion Hyperventilation attacks and dysphagia were common

The clinical course was irregular with periods of improvement interrupted by exacerbations often after increased physical exertion or during the premenstrual period By the 6th month 5 of 21 patients followed were still confined to bed and activity was restricted in many others Only 2 patients were asymptomatic Physical observations were usually normal Isolated areas of mild to moderate impairment of touch pain and temperature in varying combinations were noted in half the patients

Such a broad array of symptoms blending into a host of psychoneurotic and minor medical complaints endemic in a community makes it difficult to define the limits of the epidemic The multiple protean symptoms seem to reflect widespread disorders of function

**Epidemic Neuromyasthenia Outbreak of Poliomyelitis like Illness in Student Nurses** was studied by Alexis Shelokov Karl Habel Elizabeth Verder and William Welsh[6] (Nat l Inst of Health) This sharp outbreak of disease occurred in July 1953 among student and supervisor nurses in a private psychiatric hospital near Washington D C Typically in severe cases early manifestations included localized muscular weakness stiffness of the neck and back headache diarrhea and fever A similar epidemic had been reported in 1934 by the nursing staff of the Los Angeles County Hospital and in 1948-49 by the city of Akureyri Iceland Since then outbreaks have occurred with increasing frequency in various parts of the world including Australia Denmark England Alaska South Africa Germany and the Continental United States These epidemics differed in mi

(6) New Engla d J Med 257 345 355 A g 22 1957

nor features but had these in common occurrence usually was among the general population restricted almost exclusively to adults affecting women with greater frequency and severity or more dramatically was restricted to the nursing staff of a hospital particularly student nurses

Of 26 patients who eventually became paretic 21 presented to the Health Clinic 4-6 days before onset of muscle weakness with complaints that apparently constituted the prodrome grippelike malaise with headache achiness and low grade fever and few if any gastrointestinal complaints

The major illness began as an aggravation of the prodromal symptoms followed by some nuchal and spinal stiffness and peculiar heaviness and numbness in a limb or several extremities that became difficult to use and in which muscle strength was reduced Most commonly one or both legs were involved accompanied in many by weakness of one arm Tendon reflexes generally were normal Myalgia invariably accompanied paresis and muscle tenderness was prominent Malaise often with prostration was common Headache was often severe characteristically aggravated by sitting up unrelated to lumbar puncture Usually there was moderate nuchal and spinal rigidity Other features of the major illness were diarrhea depression instability of body temperature (2 3 degrees differential from morning temperature to afternoon) chest pain vasomotor disturbances and cutaneous sensory disturbances After early and usually misleading improvement the patient characteristically entered the subacute phase with prolonged debility Early convalescence was characterized by frequent recrudescences particularly associated with physical exertion damp and cold weather or onset of menses

Routine clinical laboratory studies were unimpressive Cerebrospinal fluid in 22 paretic and in 3 nonparetic patients was normal Complete virology studies were negative Bacteriologic studies showed two distinct types of the Bethesda Ballerup group of bacteria which were isolated from the stools of 13 patients 12 nurses who had the illness and an asymptomatic kitchen helper

Clinical findings in this clinical entity can vary between patients in any one outbreak and in different epidemic episodes The student nurses had frequent close contact with one another and perhaps even more prolonged intimate

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(6) New Engl J Med 57 345 355 Aug 22 1957

given to 20 patients were ineffective No patient died of the disease Most recovered but severe disability persisted in some for many months and 4 were still disabled at follow up

Laboratory investigations did not help in diagnosis Blood changes were nonspecific and the cerebrospinal fluid was normal Only 1 patient showed evidence of lower motor neurone degeneration Motor paralysis was accompanied by reduced motor unit potentials recruited on attempted volition with residual potentials often being polyphasic

Epidemiologic studies suggested spread by contact with an incubation period of 5-6 days Neither an infective agent nor a causative factor was found

**Periodic Disease Periodic Fever Report of Case** is presented by Kris Somers[8] (Postgrad Med School London) This syndrome of periodic signs and symptoms which elude diagnosis may occur in childhood or adult life and recur regularly over several years sometimes for a decade Various systems may be involved and symptoms so regularly cyclic as often to be predictable General health is unaffected and patients have been fully investigated without a correct diagnosis or cure Many physicians and at times unorthodox practitioners are consulted by these patients

This case is presented because of regularly occurring pyrexia for over 5 years with no convincing evidence of etiology and with no palliation

Woman 51 had undiagnosed pyrexia for 4 years She had migraine like headaches at age 17 but had always appeared to be well nourished and fit with no abnormal physical signs on several repeated careful examinations The temperature was characteristically periodic rising over a day or 2 to 102 103 F with a concomitant rise of pulse rate every 3d or 4th day falling again over a day or 2 to normal Associated with the pyrexia were headaches anorexia and malaise Rectal temperatures always confirmed simultaneous oral readings

Multiple investigations were repeated several times all resulting negatively Courses of various antibiotics were tried empirically—sulfonamide penicillin chloramphenicol and chlortetracycline all without effect One course of cortisone streptomycin isoniazid and para amino salicylic acid was continued for 9 weeks without improvement

Because of all the therapeutic failures the diagnosis of periodic fever was made to save the patient from further medical and surgical measures

► [I have seen 5 examples of this syndrome in the past 6 years In some of them there has been no real regularity of the flare ups A striking fea

(8) Brit M J 1 1086 10 8 May 11 1957

contact with their patients yet only one questionable case occurred among the patient group The hospital premises were probably the primary source of infection over a period of several months because 1 person had symptoms 6 days after leaving the hospital on vacation and 2 others became ill after returning from several weeks absence whereas a second group of cases occurred 51 days after onset of the last case in the first outbreak These considerations suggest a continuing common source of infection rather than person to person transmission

The correlation of positive isolations with clinical illness is impressive Of 38 nurses who were ill 12 excreted bacteria of the Bethesda Ballerup paracolon group, whereas none of 16 well nurses excreted these organisms during the same period If all the asymptomatic patients are included, only 1 of 54 studied excreted these organisms during the outbreaks Thus of the 13 persons from whom Bethesda Ballerup organisms were grown 12 were ill with the epidemic disease Serologic tests fix the time of initial Bethesda Ballerup infection to the time of acute epidemic illness Agglutinins of H and O types were shown indicating actual acute infection rather than chronic carrier states

Perhaps the Bethesda Ballerup strains cause this clinical disease However presence of these paracolons may merely reflect an epidemiologic situation in which fecal contamination with feces to mouth spread could occur An unknown causative agent may have been simultaneously spread by fecal contamination along with the known organisms A diligent search should be made for enteric pathogens of the citrobacter (Kauffman) group in future investigations of epidemics of this clinical entity Treatment is symptomatic

**Outbreak of Encephalomyelitis in Royal Free Hospital Group London in 1955** is described by the medical staff[7] A resident doctor and ward nurse were admitted to the wards with an obscure illness Twelve days later more than 70 staff members were similarly affected Within 4 months 292 members of the medical nursing auxiliary medical ancillary and administrative staffs were afflicted In almost every case lymphoreticular structures were involved and in three fourths the central nervous system was affected The course was fluctuating Treatment was symptomatic Antibiotics

(7) B M J 2 895 904 Oct 19 1957

signs diminished the vulvar ulcer healed and hemiparesis improved. She has had recurrent ulcers on the lips and buccal mucosa but no further genital ulcers

Sjogren s Syndrome Review of Literature and Report of Case with Achalasia of Esophagus are presented by Gerald Weissmann (United States Army Hosp Fort Dix N J) The classic clinical picture is a patient with rheumatoid arthritis who complains of blurring of vision perhaps associated with lack of tears a dry mouth and salivary gland enlargement either parotid or submaxillary Visual or salivary difficulties may antedate the arthritic complaints Parotid enlargement is usually recurrent and self limited but not necessarily bilateral The glands may be red and swollen or hard and indurated Arthritis ranges from mild early rheumatoid arthritis to severe crippling forms with typical ulnar deviation subcutaneous nodules and even spondylitis The lacrimal glands rarely enlarge There are symptoms of dysphagia cough and evidence of involvement of the secretory glands of the esophagus and trachea

Physical examination shows dry mucous membranes lack of tears and occasionally a distinctive lesion of the fingernail associated with brownish discoloration The diagnosis is made by finding superficial lesions of the cornea on rose bengal staining and by demonstrating diminished lacrimal gland response Lacrimation is decreased if less than 15 mm of a thin strip of filter paper placed under the eyelid near the gland is moistened in 5 minutes

Therapy is empiric since the etiology is unknown ACTH and cortisone relieve the associated arthritis but their effect on lacrimal and salivary secretion is equivocal The effect of any therapy is difficult to evaluate because of the variable and benign course of this syndrome

Man 44 had chronic disabling arthritis of knees hands interphalangeal joints hips elbows shoulders and costosternal articulations for 4 years Bilateral swelling of the parotid glands was present for 3 days He had epigastric distress noted that food would stick in his chest and was aware of lack of tears He was not aware of diminished saliva but had noted visual difficulties occasional blurring of vision and drying of the eyes for several months

The parotid glands were bilaterally diffusely enlarged and palpable giving a pouchlike appearance to the angle of the jaw and were red and swollen The mouth showed fissures and cracking of both lips slight superficial ulcerations of the inner lip margin and marked

(2) Am J M d 24 475 481 M b 1958

ture is that the general health remains good even after a great many episodes of acute illness —Ed ]

**Periodic Fever Occurrence in Five Generations** is reported by Bertha A Bouroncle and Charles A Doan[9] (Ohio State Univ ) Periodic fever is not merely a medical curiosity Correct diagnosis is important for proper medical therapy Cortisone relieved the symptoms in the 3 patients to whom it was given

CASE 1 —Man 52 since birth had recurrent fever every 21 28 days lasting 3 5 days with chills temperatures to 103 F malaise constipation and stiffness and soreness of all joints Each episode required confinement to bed No detectable external influence subjective emotional factor or food idiosyncrasy could be related to the attacks Between attacks he was well but during the febrile episodes he was acutely ill the conjunctivas were injected and the skin showed irregular and circular erythematous lesions Blood studies were normal Stool blood and urine cultures and agglutination studies were negative Chest and skull x rays were normal Serum electrophoresis showed increased alpha and gamma globulin

CASE 2 —Youth 17 son of the patient in Case 1 had periodic fever lasting 3 5 days every 21 28 days

CASE 3 —Man 82 father and grandfather of the other 2 patients had similar attacks of fever as long as he could remember Between attacks he was alert and appeared normal

The 5 sisters of the oldest patient his other son and 1 of his 2 granddaughters all have periodic episodes of fever with similar characteristics In this family periodic fever is apparently inherited probably as a dominant autosomal gene

**Case of Behçet s Syndrome with Neurologic Involvement** Relapsing iritis oral ulceration and genital ulceration constitute the basic triad of a specific syndrome but wider manifestations e g neurologic and skin lesions arthralgia and thrombophlebitis have been reported Rhys T Williams[1] (Paddington Gen l Hosp London) reports a case

Woman 42 had severe shoulder pain followed 2 weeks later by dysuria and vulvar soreness due to an ulcer and later by small slightly painful ulcers on the lips Her legs felt weak and the left arm and leg became paralyzed Examination showed left hemiparesis without sensory loss and ulcers on the lower lip and labium minorum The cerebrospinal fluid contained 64 lymphocytes/cu mm and 60 mg protein/100 ml

Symptoms and signs progressed and she had a numb feeling in the tongue lips and nose Nystagmus and bilateral facial and right palatal weakness were apparent Under observation the brain stem

(9) Am J M d 3 502 506 S ptemb 1957
(1) Brit M J 1 384 F b 15 1958

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(2) Am J Med 24 475 481 Ma ch 1958

xerostomatitis Interphalangeal joints of both hands were hot and swollen and both wrists were markedly swollen with residual deformity and slight ulnar deviation The right ankle and both shoulders were hot and painful and the sternoclavicular junctions were red and swollen He had punctate staining spots on both corneas and slight conjunctival injection A Schirmer test showed no tearing response (0 5 1 mm of the paper became wet in 5 minutes) pathognomonic of keratoconjunctivitis sicca

If this syndrome were better known the true incidence might become apparent Perhaps an understanding of the elements involved in Sjogren s syndrome—lacrimal and salivary gland malfunction lymphocytic infiltration achlorhydria and other manifestations—would elucidate the connective tissue disorder that is rheumatoid disease –

**Radiologic Aspects of Reiter s Syndrome ( Venereal Arthritis)** This disease is characterized by urethritis arthritis and sometimes involvement of the skin mucous membranes and eye D F Reynolds and G W Csonka[3] (St Mary s Hosp London) reviewed the findings in 185 patients with venereal arthritis who attended the Venereal Disease Clinic from 1942 to 1956 Of these 25 showed only arthritis apart from the genital infection and 35 also showed changes in the eye and skin The specific features of radiologic interest were predilection for the joints of the lower limbs Achilles tendinitis and patellar tendinitis Achilles tendinitis in particular occurred more often in venereal arthritis than in any other condition Rheumatoid arthritis represented the major diagnostic difficulty

Certain radiologic features though occasionally seen in rheumatoid arthritis should arouse suspicion These are edema of the Achilles or patellar tendons periosteal new bone formation adjacent to a metatarsophalangeal joint spurs on the plantar aspect of the os calcis rheumatoid arthritis in a male with feet more seriously affected than hands and sacroiliitis preceded by peripheral arthritis and without spinal involvement

**Visna a Demyelinating Transmissible Disease of Sheep** Sporadic cases of a central nervous system disease of sheep were reported during 1935 51 in Iceland Bjorn Sigurdsson Pall A Palsson and Halldor Grimsson[4] (Univ of Iceland) studied a number of affected sheep between 1949 and 1951

Visna is insidious *in its onset appearing first as a slight*

(3) J Fac Rad log t 9 44-49 J n ry 1958
(4) J Neuropath & Exper N l. 16 389-403 J ly 1957

aberration in gait The head is kept in an unnatural position and there is a fine trembling of the lips These symptoms gradually progress and may lead to paraplegia or total paralysis and eventual death Fever is low or absent The cerebrospinal fluid shows pleocytosis (mostly lymphocytes) and increased protein With appropriate preparations of infected brain and cord material the disease may be transmitted to healthy animals who then have high cell counts in the cerebrospinal fluid for several months without clinical signs Once clinical signs appear the course continues relentlessly to paralysis and death The disease could not be transmitted to mice hamsters guinea pigs or rabbits The virus survived in infected brains which were kept frozen at —22 C for as long as 30 months

Histologic changes in the central nervous system are conspicuous mainly as demyelination and destruction of white matter in the brain cerebellum and spinal cord

The successive stages of the disease follow each other regularly resembling the well known acute infections but the infection develops so slowly that over 26 months may elapse after effective transmission until clinical signs appear It is puzzling that this low grade infection which produces the pleocytosis in the cerebrospinal fluid should continue unchecked by the host s mechanism of immunity for many months ending in a severe crippling disease Apparently the body s defensive mechanism is ineffective

The active visna principle sediments in the ultracentrifuge and may be washed there repeatedly

► [This disease of sheep is of possible interest to us because of its long course and re emblance to multiple sclerosis Investigators elewhere hesitate to undertak its study lest it become established in other parts of the world —Ed ]

**Clinical Manifestation of Histiocytosis X in Adult** are reviewed by John L Dadey and Lewis M Hurxthal (Lahey Clinic) The three syndromes of eosinophilic granuloma Hand Schuller Christian disease and Letterer Siwe disease are now considered to be interrelated manife tations of a single malady Eosinophilic granuloma is relatively benign with single or multiple skeletal lesions primarily proliferation of histiocytes and eosinophils The Hand Schuller Christian syndrome is characterized by multiple round defects *in the skull unilateral or bilateral exophthalmos and*

(5) J Ch D 6 475 48 N mb 1957

diabetes insipidus One or 2 of these abnormalities may exist combined with other manifestions The Letterer Siwe syndrome which occurs almost exclusively in children particularly under age 3 is an acute entity associated with acute clinical manifestations

The organs or systems chiefly involved in histiocytosis X are the bones brain lungs skin reticuloendothelial system and mucous membranes The disease may simulate a variety of disorders neoplasms of the brain orbit and bones chronic infections such as tuberculosis particularly if the lungs are involved and cough night sweats and weight loss are present periarteritis nodosa sarcoidosis Hodgkin s disease pneumoconiosis amyloidosis and similar diffuse diseases When certain characteristic combinations of signs are present such as diabetes insipidus exophthalmos multiple bony lesions skin lesions the diagnosis may be suspected Definitive diagnosis however depends on histologic examination of the involved tissue

► [Probably not an infection but included because its clinical features may resemble those of other disorders which are grouped in this section of the YEAR BOOK —Ed ]

## MATERNAL VIRUS INFECTION AND CONGENITAL DEFECTS

**Frequency of Defects in Infants Whose Mothers Had Rubella during Pregnancy** was investigated by Morris Greenberg Ottavio Pellitteri and Jerome Barton[6] (New York) A prospective study was carried out in 1949 55 and follow up information collected on 104 pregnant women who had developed rubella The association between rubella in a pregnant woman and birth of a malformed infant has been stressed so strongly and advertised so widely that many physicians and pregnant women assume that one is necessarily followed by the other As a result therapeutic abortions are advised by physicians and demanded by pregnant women Previously rubella during the first 2 months of pregnancy was considered to lead to 100% congenitally defective infants Such astounding percentages have been accepted by physicians as authentic rates The main objection to this type

(6) J A M A 165 675 678 Oct 12 1957

of study however is statistical No consideration is given to children who were born normal and who therefore were not studied If 100 pregnant women give birth to 100 infants 10 of whom are deformed incidence is 10% If the inquiry starts with the 10 deformed infants and works back the finding will be that all the mothers had rubella during pregnancy and this may thoughtlessly be construed as 100% incidence

Incidences of congenital malformations reported by earlier workers are fantastically high and incorrect The recommendation of therapeutic abortion based on those rates is not medically justified Rubella early in pregnancy is associated with congenital deformities in the offspring but the degree of association has not yet been determined Incomplete data indicate a rate of about 12% which is vastly different from the 90 100% reported in retrospective studies

There is quite a difference between informing a woman she has a 90% chance of having a normal baby and informing her she has 90 chances out of 100 in having a deformed baby If the woman is young already has 1 2 children and has no difficulty conceiving she may not want to take the added risk even though it is not large However an older primipara particularly one who has difficulty conceiving might be willing to assume the smaller risk At any rate it is scientifically unsound and medically unjustified to state that risk is higher than the facts warrant

► [This seems to me to be a sound point of view worthy of emphasis —Ed ]

**Congenital Defects in Infants Following Mumps during Pregnancy Review of Literature and Report of Chorioretinitis Due to Fetal Infection** is presented by Jean Holowach Don L Thurston and Bernard Becker[7] (Washington Univ ) Rubella infection during the first trimester is generally accepted as a possible cause of fetal death or congenital malformation but relation of maternal mumps to fetal damage is less certain In the literature mumps in the mother during pregnancy has been related to stillbirth congenital abnormalities such as bilateral corneal opacities imperforate anus spina bifida occulta urogenital deformity organic nerve disease of Little type mongolism congenital abnormality of the ear hypospadias congenital cardiopathy fetal meningoencephalitis monster and intestinal atresia

(7) J P d t 50 689 694 J 1957

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(6) J A M A. 165 675 678 O t 12 1957

loma globulin Recurrent pneumonia is an indication of this lowered resistance Reports in the literature include one on 10 patients with multiple myeloma who had pneumonia a total of 44 times with the individual patient having from 2 to 13 bouts In 3 patients the same type of pneumococci as originally isolated during pneumonia later caused recurrences in 1 after more than 2 years For the 1st episode each patient had been treated with penicillin

► [Clinical rule multiple attacks of pneumonia in a patient pa t 50 calls for search for multiple myeloma —Ed ]

**Treatment of Bacterial Infections with Combination of Antibiotics and Gamma Globulin** Some of the patients treated did not respond to maximum efforts of therapy with more conventional methods The first 3 seemed to be progressing inextricably toward complete invalidism and early death Their dramatic response to the use of gamma globulin with the antibiotic led Burton Armin Waisbren[9] (Marquette Univ ) to investigate 46 other patients

CASE 1 —Man 49 had chronic osteomyelitis of the thoracic vertebra after trauma Needle aspiration of the left lumbar area produced pure pus which grew Staphylococcus aureus coagulase positive Vigorous and specific therapy for 3 years was ineffective His response to oral chloramphenicol and intramuscular gamma globulin was striking

CASE 2 —In man 71 osteomyelitis of the lumbar spine developed because of bacteremia after operation for a herniated intravertebral disk Blood culture at that time grew Staph aureus Three years later he again became febrile and had severe back pain X rays revealed extensive destruction of the 5th lumbar vertebra likely due to a postoperative osteomyelitis Vigorous therapy with Novobiocin erythromycin streptomycin and neomycin was ineffective but when oral chloramphenicol intramuscular gamma globulin and intramuscular streptomycin were given the infection was apparently controlled Chloramphenicol and streptomycin were not tried alone before gamma globulin was added

CASE 3 —Man 53 had osteomyelitis of the 2d and 3d lumbar vertebrae due to Salmonella typhimurium Chloramphenicol and tetracycline given together were ineffective He responded to chloramphenicol and gamma globulin

CASE 5 —In woman 65 a fluctuant mass appeared over the operative site 6 month after her left hip had been pinned Pus was aspirated which grew coagula e positive Staph aureus Chloramphenicol given alone had no apparent effect When gamma globulin was also given the infection was rapidly controlled

These results indicate that in certain instances the addition of gamma globulin to antibiotic therapy may give clin

(9) A t b t & Ch m th 7 32 333 J 1957

Nurse 28 whose last menstrual period was Mar 11 1954 developed mumps 3 months later On December 18 she delivered spontaneously a 6 lb 12 oz infant Since birth the baby s eyes crossed in and eye movements were purposeless with inability to focus This was mentioned to her physician before discharge and she was reassured

At age 6 months the infant was normally responsive well nourished and well developed The eyes showed a searching type of nystagmus the pupils reacted sluggishly to light the media were clear Disks were markedly atrophic the left was about one half the size of the right Atrophic scars with peripheral pigmentation were noted in the macular region of the eyes with another area of atrophy between the left disk and the macula The fundi were peculiarly mottled bilaterally Congenital toxoplasmosis was excluded by serum testing

Fetal mumps virus infection seems certain in this patient Its relation to chorioretinitis was not proved but the association is highly probable

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## GAMMA GLOBULIN AND INFECTION

**Recurrent Pneumonia in Multiple Myeloma Due to Acquired Functional Hypogammaglobulinemia** A case is reported by Sven Åge Killmann and Else Ehlert Knudsen[8] (Univ of Copenhagen)

Man 69 with myelomatosis had 9 acute attacks of pneumonia in the 3 years after diagnosis was established Prophylaxis with penicillin was of some benefit because subsequently he had only 2 acute attacks of pneumonia

Clinically this conditions resembles hypo or agammaglobulinemia The large amount of gamma globulin in patients with multiple myeloma (myeloma protein) apparently does not participate in humoral defense mechanisms Concentration of normal antibody carrying gamma globulin might be decreased because of interference of antibody globulin formation by production of the myeloma protein This was substantiated by a test in which the patient was given 3 injections of suspension of killed Salmonella typhi and S paratyphi A B and C The Widal test remained negative after this immunization

Decreased resistance to infections in patients with multiple myeloma is common and is due to reduced concentration in the serum of antibody carrying normal gamma globulin despite high total gamma globulin content due to the mye

(8) D n b M d B ll 4 153 155 Aug 1 1957

blood cells counts ranged from 150 to 72 000 (average 22 000)

Sixteen bacteremias were introduced via the genitourinary system 11 following urethral manipulation Six entered via the respiratory tract 4 the biliary tract and in 10 the portal was unknown Antibiotic therapy did not differ significantly in those who survived and those who did not Methoxamine (Vasoxyl®) was used in 9 patients but 8 had no response and only 1 showed a rapid elevation of blood pressure to normal levels Levarterenol bitartrate (Levophed®) was used in 26 patients and 21 had an excellent response

The clinical picture was variable 16 patients were flushed and most of the others were cold and clammy to touch There was no apparent difference in the organisms ability to produce one or the other picture This probably depends on the susceptibility of the host Laboratory findings were generally consistent with a severe infection All but 5 had white blood cell counts over 10 000 and 18 over 20 000

Therapy could not be evaluated Large doses of antibiotics were used in all the patients Blood fluids and electrolytes generally failed to have noticeable effect and the only vasopressor agent which gave satisfactory results was levarterenol It was used continuously for as long as 5 days but generally could be discontinued after 18 24 hours The results of steroid therapy were indeterminate

► [Our experience has been similar levarterenol is the most effective vasopressor agent. Hydrocortisone given intravenously may be a helpful adjunct we think —Ed ]

**Bacteremia and Shock in Urology** are frequent Operative and manipulative trauma to extremely vascular areas often the locus of virulent micro-organisms must produce bacterial invasion of the blood stream far more often than recognized When the bodily defense are overwhelmed high temperature hypotension and peripheral vascular collapse are seen William H Rattner and John J Murphy[2] (Univ of Pennsylvania) report 3 cases and formulate a rational method of therapy

CASE 1 —Man 62 with acute urinary retention had a transurethral resection complicated by secondary hemorrhage requiring suprapubic cystostomy Within 3 hours his temperature rose to 106 4 F

(2) J U I 77 875 879 Ju 1957

ical results that could not be obtained with antibiotics alone Dose of gamma globulin was 10 ml daily or every other day Long and extensive control periods of vigorously ad ministered antibiotics were ineffective but when gamma globulin was given with about the same doses of antibiotic improvement was marked Gamma globulin alone probably would not have shown comparable results

The mechanism of this phenomenon is unknown Studies of serum proteins and electrophoretic patterns before and after therapy did not indicate hypogammaglobulinemia nor was any change evident after fairly large doses of gamma globulin

► [Some of the case reports are impressive More experience with this is desirable —Ed ]

## BACTEREMIC SHOCK

*Bacterial Shock Clinical Analysis of 38 Cases* According to Joseph A Ezzo and William A Knight Jr[1] (St Louis Univ ) shock is fairly common with gram negative some what less with gram positive bacteremias The mechanism seems to be the same Clinical criteria are systolic blood pressure under 85 mm Hg and a positive blood culture

Of 37 cases caused by a single organism (table) 14 were due to gram positive cocci and 23 to gram negative bacilli Rectal temperatures ranged from 94 to 107 4 F Of the 38 patients 27 were febrile and 21 had shaking chills White

CAUSATIVE BACTERIA

| O G | Ca | Dea hs | Ma e | Fe e | Ag |
|---|---|---|---|---|---|
| Staph aureus | 8 | 6 | 6 | 2 | 2ɔ 77 |
| Ps aerugino a | 8 | 5 | 5 | 3 | 45 88 |
| A aerogenes | 3 | 1 | 2 | 1 | 52 84 |
| Staph albus | 2 | 1 | — | 2 | 2ɔ 67 |
| E coli | 6 | 5 | 4 | 2 | 48 85 |
| Pneumococcus | 3 | 2 | 2 | 1 | 48 64 |
| Enterococcus | 1 | — | 1 | — | 55 |
| Proteus | 5 | 3 | 4 | 1 | 50 85 |
| Klebsiella | 1 | 1 | — | 1 | 55 |
| Mixed | 1 | 1 | — | 1 | 31 |
| E coli | | | | | |
| Staph aureus | | | | | |
| Total | 38 | 2ɔ | 24 | 14 | 25 88 |

(1) A M A A h Int M d 99 701 707 M y 1957

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CASE 1 —Man 62 with acute urinary retention had a transurethral resection complicated by secondary hemorrhage requiring suprapubic cystostomy Within 3 hours his temperature rose to 106 4 F

(2) J Urol. 77 875 87) June 1957

the blood pressure dropped from 160/90 to 100/60 mm Hg and then to 85/55 mm Hg He had shaking chills and appeared cold and clammy A blood culture showed *Aerobacter aerogenes* The white blood cell count was 55 800 He was treated with vasopressors steroids and oral antibiotics and made an uneventful recovery

CASE 2 —Man 76 with acute urinary retention required a supra pubic cystostomy 24 hours later he was disoriented his temperature was 105 6 F rectally his blood pressure was 80/60 and he had constant shaking chills He was treated with intravenous chloram phenicol phenylephrine and hydrocortisone and later oral medica tions He recovered

CASE 3 —Woman 43 had a temperature of 104 F 12 hours after a ureteral catheter was passed accompanied by shaking chills and a white blood cell count of 59 000 The blood pressure was unobtainable Coliform organisms were isolated from the urine and the peripheral blood She was treated with levarterenol chloramphenicol and cortisone and recovered

Adrenal insufficiency could not be proved in these cases because laboratory data were lacking However clinically addition of adrenal steroids led to rapid improvement The most satisfactory therapeutic program includes blood and intravenous fluids antibiotics vasopressor agents and ad renal support in the form of hydrocortisone 100 mg/L every 12 hours

## ANAEROBIC CULTURES

**Anaerobes in Routine Diagnostic Cultures** In many hos pital laboratories cultures are made in air as a routine and the specimen is not investigated for anaerobes unless there is some special indication Logically the reverse procedure would be more reasonable because strict anaerobes are com mon and strict aerobes are rare in medical bacteriology Re cently the McIntosh and Fildes jar has been so modified that it is quicker and simpler to use If anaerobic cultures are desirable there is no longer any technical reason for not including them routinely

E Joan Stokes[3] (Univ College Hosp London) by using the McIntosh and Fildes jar cultures routinely found that of 4 737 specimens yielding growth 496 yielded anaerobes and 139 of these were pure cultures of anaerobes If anaerobic culture had not been made routinely these would have been

(3) Lancet 1 668 670 Mar 29 1958

reported sterile From every type of specimen studied anaerobes were recovered at one time or another (table)

Anaerobes have long been known to form a large part of normal human flora Finding them frequently in pus is no new discovery When no specific treatment was available *there was little point in isolating these delicate and slow* growing organisms With antibiotics the nonsporing an

ANAEROBIC STRAINS ISOLATED FROM VARIOUS SOURCES

| Specimen | Positive cultures | Tot l no yi lding anae obes | Ana robes in pu culture | Percentage yielding ana robes |
|---|---|---|---|---|
| Pleural fluid | 144 | 18 | 10 | 12 5 |
| Ce b o p nal flu d | 33 | 3 | 2 | 9 0 |
| *Blood* | *85* | *9* | *8* | *10·5* |
| Abd minal pus | 5 8 | 173 | 30 | 32 7 |
| Ge t l pus | 2 0 | 69 | 24 | 31 3 |
| Neck lymph-gland | 101 | 8 | 3 | 8 0 |
| Inf ed ba ou cyst | 66 | 21 | 13 | 31·0 |
| Boils & | 1339 | 18 | 4 | 1 3 |
| Other | 2.21 | 177 | 45 | 7·9 |

aerobes can no longer be ignored These are constantly pres ent in the human intestine upper respiratory tract and gen ital passages and can infect sometimes fatally when they invade unfamiliar sites

Nonsporing anaerobes particularly gram negative bacil li cannot always be seen in the stained films of specimens which subsequently yield heavy growth Liquid cultures are unsatisfactory because these organisms are easily outgrown Routine primary culture on blood agar in an anaerobic jar is essential If for reasons of economy only one plate culture can be made an anaerobic is preferred because strict aerobes are extremely rare

► [It is unfortunate that we tend to ignore anaerobes in routine clinical bacteriology in this country Undoubtedly this leads to errors such as re ports of sterile pus or to treatment being directed at an associated but unimportant aerobe Thioglycollate medium is an inadequate substitute for culture on solid mediums incubated anaerobically —Ed ]

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## THINGS NOT WHAT THEY SEEM

Factitious Fever Robert G Peter dorf and Ivan L Ben nett Jr[4] (John Hopkins Univ ) describe 14 cases of fever *of unknown origin in which the abnormally high temper*

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(4) A n I t M d 46 1039 106 Ju e 1957

atures were probably fraudulent 12 were in women of whom 5 were nurses Several clues may suggest that the fever is *spurious* (1) failure of the temperature to follow the normal diurnal gradient of body temperature—higher in the late afternoon and early evening (2) absence of tachycardia accompanying the temperature spikes (3) strikingly rapid defervescence unaccompanied by diaphoresis and (4) temperature of 106 F or higher a relatively rare phenomenon in adults

Nurses doctors and others familiar with hospital routine *are particularly skilful at this form of malingering* Technics of falsifying the temperature are many and varied sometimes ingenious The common methods are holding the thermometer next to a hot water bottle steampipe light bulb or flame rubbing the instrument against the bedclothes shaking it in retrograde fashion and manipulating the teeth gums or anal sphincter to produce friction A more sophisticated maneuver is to keep a cache of thermometers set at various readings and to substitute one of these for the one distributed by the nurse

Spurious fever is often associated with other factitious disease It may be difficult to decide whether the fever is fraudulently induced or whether the elevation in temperature is genuine but secondary to some other artefactual lesion Before facing the diagnostic enigma so often presented by a case of F U O be sure the F component is present Once the hoax is discovered management is a serious problem These patients often wander from hospital to hospital and characteristically leave against advice when the truth becomes known and psychiatric treatment is suggested

**Overgrowth of Serratia Marcescens in Respiratory Tract Simulating Hemoptysis** Report of Case is presented by David Gale and John D Lord (Durham N C) Prolonged use of broad spectrum antibiotics may alter normal flora of the body and antibiotic sensitive organisms may be replaced by organisms *usually* considered nonpathogenic that may set up new infectious syndromes Serratia marcescens (Chromobacterium prodigiosum Bacillus prodigiosus) is an aerobic motile gram negative rod that produces red *pigment insoluble* in water It generally is considered saprophytic with no known pathogenicity for animals or man

(5) J A M A 164 13 8 1330 J ly 20 19 7

Man 39 was admitted with severe asthma after treatment with various drugs including antibiotics Cortisone was started On the 11th day temperature was 102 F and he had pain in the left lower chest. White blood count was 14 100 On the 17th day blood streaked sputum was noted. The next day he was coughing up mouthfuls of bloody sputum X ray study showed no change Sputum cultured large quantities of S marcescens Sputum examination showed no red blood cells and no occult blood by benzidine or guaiac tests

This organism is weakly pathogenic With modification of the host defenses by steroids or antibiotics or other factors organisms normally considered nonpathogenic may become pathogenic for a particular person

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## BASIC INVESTIGATIONS

**Microbial Persistence** Many animal species play dead when confronted with a hostile threat Walsh McDermott[6] (Cornell Univ ) considers the adaptability of microbes to their environment to be such that they too can play dead when menaced by an antimicrobial drug

The term *microbial persistence* is used to describe a phenomenon whereby micro-organisms which are drug sus ceptible when tested outside the body can survive within the body despite intensive therapy with the appropriate anti biotic Clinically this phenomenon is a factor in the post treatment carrier state and in posttreatment relapse It was not recognized until the introduction of penicillin The early antimicrobial drugs quinine arsphenamine Atabrine® and sulfonamides could not be given in large doses because of toxicity and bacterial survival was considered due to this rather than to the adaptive plasticity of the microbes

Microbial persistence for many weeks despite exposure to the appropriate antibiotic cannot be explained by drug re sistance as experiments showed that the microbes were not resistant when cultured again Drug dosage is a second pos sibility and a third is the barriers in the tissue in the form of fibrotic walls avascular areas or walls of leukocytes or phagocytes However drug transfer has been demonstrat ed through the fibrous walls and even intracellular microbes are influenced by penicillin The ability of a few intracellular staphylococci to survive is not a result of failure in delivery

(6) Yale J Biol & Med. 30 257 291 February 1958.

of penicillin to the interior of the cells A fourth possibility that inflammatory lesions exert an antagonistic influence on the antimicrobial drug is no longer tenable In treating human beings it is distinctly improbable that differences in diffusion gradients materially impede complete impregnation of the lesion Protein binding is easily reversible and the degree of binding depends on the concentration of drug in the immediate environment Thus even if macromolecular binding were occurring quantities of drug would also be released depending on the surrounding concentration

Environmental changes influence drug effectiveness and may well antagonize drug activity but seldom if ever can this antagonism attain the magnitude which would satisfactorily explain the phenomenon of microbial persistence It must be the parasite which can assume a state in which it is neither permanently incapacitated by the drug nor able to multiply freely in the presence of the drug The organisms are considered drug indifferent as contrasted with the drug resistant bacteria which grow freely in the presence of the drug

It is not the age of the microbial population per se but its adaptive changes to the environment which are associated with its drug indifference This is not identical with saying that penicillin acts only on multiplying bacteria The latter implies that the metabolic state which leads directly to cell division is *ipso facto* the state in which the microbial cells can be killed by penicillin In the proposed explanation multiplication or cell division is only a side issue As young microbes grow they lose something or gain something which makes them resistant to drugs and this is induced or favored by the influence of the environment on the microbe

The characteristic tissue changes produced by tubercle bacilli or staphylococci are not seen in animals harboring drug persisters Microbial persistence can occur without evoking the host immune response characteristic of that particular infection

The microbial persisters during hibernation probably are different Several recent studies have shown that the L-forms or protoplasts of certain microbes have a definite bearing on the action of penicillin When the cell wall of a bacterial cell is lysed the cytoplasm and limiting membrane may continue

to exist as the so called protoplast Several investigators have shown with Escherichia coli and Proteus vulgaris that protoplasts can be induced regularly by appropriate exposure to penicillin and that the protoplasts are not destroyed by penicillin When the penicillin is removed from the environment the protoplasts revert to the vegetative (and penicillin susceptible) form Thus biologic precedents have been demonstrated for every step of the argument that microbes possess an adaptive plasticity in relation to their environment which permits them to persist in the animal body despite exposure to the appropriate antimicrobial drug

Microbial infections (including drug resistant cells) can become dormant or truly latent in an animal by natural processes and not only after antimicrobial therapy Microbial persistence despite drug therapy is probably due to mechanisms similar to those which permit infections to become dormant or latent when no therapy has been given Some evidence indicates that when a microbial population first infects a new host some members of the population are drug indifferent and can be kept in that state as long as appropriate antimicrobial therapy is administered

Published observations on five infectious diseases in human beings (syphilis malaria scrub typhus tuberculosis and Q fever) indicate that antimicrobial therapy started very soon after inception of the infection does not eradicate it but holds the situation static as long as administration is continued Apparently there is a stage to which the host parasite reaction must mature before the infection is fully drug susceptible Presumably a portion of the population is and remains drug indifferent When members of this group become more drug susceptible or are newborn into such a state they are presumably immediately incapacitated by the antimicrobial drug present in the environment

Whether microbial persisters are actively drug induced or arise only as an evolutionary adaptation to their environment is still not settled It can be inferred however that microbial persistence can occur right from the early stages of an infection before environmental changes due to microbe host interaction would be too advanced and that the over all effectiveness of an antimicrobial drug is maximum when the infection is actually producing disease

Microbial persistence occurs broadly throughout the microbial world even without antimicrobial therapy It is its occurrence despite antimicrobial therapy that makes understanding this phenomenon of such importance in considering treatment failures posttreatment relapse and the chemoprophylaxis of either infection or its subsequent individual manifestations as disease It is believed that the range of microbial adaptation in vivo is substantial and that this capacity of individual microbes to express individuality determines largely the success or failure of antimicrobial therapy

► [An interesting and stimulating summary of work done on this problem by Dr McDermott and his associates over a period of several years —Ed ]

**Value and Duration of Defense Reactions of Skin to Primary Lodgement of Bacteria** were studied in the guinea pig by A A Miles Ellen M Miles and J Burke[7] (London) In all animal infections the infecting microbes take advantage of a breach in the surface defenses of the host to lodge in or on the tissues Subsequent suppression or eventual growth into an infection is determined in part by the antimicrobial properties of the tissues immediately surrounding it These tissue responses heretofore have not been studied

Infection was enhanced by local injections of epinephrine Initiation of 2 hours of local epinephrine ischemia or 2 3 hours of general dehydration shock at time of intracutaneous injection of certain bacteria substantially *increased* the maximal size of the local infective lesion equivalent to *increasing the infecting dose by a factor of 10 to 10*[6]

After infections were several hours old local epinephrine Liquoid® or general dehydration shock had no effect Apparently at this stage the defenses previously inhibitable no longer have any decisive effect on subsequent development of the lesion This short decisive period applies also to the bacteria in the lesions and is common to a number of experimental skin infections Infections 3 5 hours old were not susceptible to intravenous antibiotics in doses otherwise effective when given earlier in the infection At this stage blood supply to the lesion was not obstructed

In general Bacterium coli Pseudomonas pyocyanea Proteus vulgaris and Clostridium welchii were most strongly enhanced Streptococcus pyogenes and Staphylococcus aureus less and Corynebacterium diphtheriae C ovis and Listeria

(7) Brit J Exper Path 38 99 96 February 1957

monocytogenes were only moderately enhanced Bactericidal agents in the blood apparently are inhibited from gaining access to the lesion or their action in the lesion is altered Degree of enhancement is in general correlated with susceptibility of the pathogen to the bactericidal action of blood and serum in vitro

[This work by A A Miles and associates contributes important information to our knowledge of acute infections The demonstration that the ultimate course of an infection is determined largely by events taking place during the first 2 hours after introduction of the infectious agent—the decisive period —should lead to better understanding of host defense mechanisms —Ed ]

**Diphosphopyridine Nucleotidase as Extracellular Product of Streptococcic Growth and Its Possible Relationship to Leukotoxicity** Hemolytic streptococci produce a protein that inhibits oxidation of citrate fumarate and alpha keto glutarate by mitochondria and specifically catalyzes cleavage of diphosphopyridine nucleotide (DPN) at the nicotinamide ribose linkage To determine whether this nucleotidase (DPNase) accompanies growth of bacteria in general or is uniquely associated with streptococci Alan W Bernheimer Penelope D Lazarides and Armine T Wilson[8] examined the DPNase activity of culture supernates of diverse bacterial species and a series of streptococcic strains

Of 170 streptococcic strains 98 yielded supernates that contained DPNase These strains all belonged to group A C or G Of group A streptococci 41 strains had pedigrees suggesting that they were the etiologic agents of acute glomerulonephritis and 39 of these produced DPNase In contrast 3 species of yeasts and 42 of bacteria other than streptococci of the Lancefield groups produced no DPNase as an extracellular product of growth

The mechanism by which streptococci injure leukocytes is unknown but apparently depends on elaboration of a specific toxic substance The toxin does not appear to be identifiable with any previously studied streptococcic product such as erythrogenic toxin streptolysins streptokinase leukocidin etc The remarkable qualitative correlation between DPNase production and leukotoxicity suggests that these two functions are associated and perhaps may be identical After ingestion of leukotoxic streptococcus DPNase may pass from the coccus into the substance of the phagocytic

(8) J Exp Med 106 27 37 July 1957

cell and there produce rapid destruction of DPN resulting in death of the phagocyte

**Similarity of Host Responses Elicited by Polysaccharides of Animal and Plant Origin and by Bacterial Endotoxins** Endotoxins of gram negative bacteria can elicit fever leukocytic changes Shwartzman s phenomenon damage to tumors vasomotor disturbances collapse and death The preparations with these capacities were all of high molecular weight and contained polysaccharide moiety Products from animal tissues also may elicit one or another of these responses Maurice Landy and Murray J Shear[9] (Nat l Inst of Health) with assistance of Robert John Trapani and Adrian Perrault systematically investigated 10 polysaccharides of plant and animal origin for their biologic properties and compared them with typical endotoxic polysaccharides from 2 species of gram negative bacteria for capacity to elicit these reactions

The tissue sources were mouse (kidney liver lung stomach sarcoma 37 and carcinoma 241 6) rabbit and chick embryo skin and tangerine and bryonia root Bacterial endotoxins were from Salmonella typhosa and Serratia marcescens Some of the polysaccharides were consistently active in all the host reactions studied Except for pyrogenic activity at high dosage the other polysaccharides were consistently negative Mouse tissue polysaccharides elicited all the effects studied sometimes with potency approaching that of the bacterial polysaccharides

Results showed that certain polysaccharides derived from mammalian and plant sources evoke a variety of disturbances such as fever leukocytic changes the Shwartzman phenomenon tumor damage dermal hemorrhagic necrosis by epinephrine enhancement of antibody production and at sufficiently high doses fatal collapse This combination of effects previously was considered unique to bacterial endotoxins

► [This work demonstrating that tissues of animals contain polysaccharides with properties similar to those of bacterial endotoxins may serve to enhance the importance of the vast amount of study that has been devoted to the biologic effects of bacterial endotoxins —Ed.]

(9) J Exper M d 106 77 97 July 1957

# THE CHEST

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CARL MUSCHENHEIM M D

## PART II

# THE CHEST

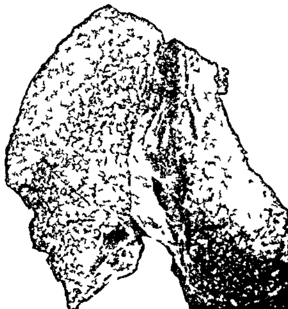
## PATHOLOGY AND EXPERIMENTAL PATHOLOGY

**Bronchiolar Emphysema So called Cirrhosis of Lungs** Two more cases are reported by Frank T Siebert and Edwin R Fisher[1] (Univ of Pittsburgh) bringing to 12 the total documented in the world literature Clinical features are progressive dyspnea chronic unproductive cough and cor pulmonale Grossly the involved portions of the lungs have finely bosselated and fibrous external surfaces (Fig 16) resembling the liver in Laennec s cirrhosis The cut surfaces present many small air containing cysts 1 3 mm in diameter interposed among dense and apparently imperfectly aerated pulmonary tissue Microscopically the respiratory bronchioles are markedly dilated and the muscular coats hypertrophied (Fig 17) Alveoli are diminished inconspicuous or absent and areas of fibrosis frequent

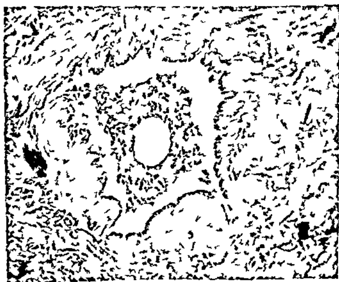
The pathologic process exhibits intricate patterns of groups of interconnecting rounded or asymmetrical cysts of varying size Each group consists of a dilated proximal respiratory segment composed of a single respiratory bronchiole and its appendages with hypertrophy of the bronchiolar muscularis impairment of its elastica and fibrosis Many proximal segments end as blind multibulbous sacs forming abbreviated respiratory units These are embedded in a dense fibromyoela tic matrix composed of stenotic hypoplastic distal segments or the residual stroma derived from the obliteration of such structures In advanced stages gas exchange cannot occur

The pathogenesis of bronchiolar emphysema is complex Apparently three separate predisposing factors must all be present (1) hypoplasia of the distal segment of the respiratory unit (2) inherent structural weakness of the myoelastic

(1) Am J P th 33 1137 1161 N Dec 1957



F g 1 — C rh t c ppe c f xtern l u fa e f lu g (Co te y of Si be t F T d F h E R Am J P th 33 1137 1161 N v De 1957 )



F 17—Cy t c re p t ry L onch l l ng m k d hypert phy f m scu l r ( gm t t n f laste nd l m n l d \ hoeff G son et re d ce l f m ×140 (Co rte of S bert F T d F h r E R Am J I th 33 113 1161 No Dec 1957 )

wall of the upper respiratory bronchiole and (3) the pathophysiologic components which enhance this weakness The first is unique and is the crucial factor which predetermines that the lesions of bronchiolar emphysema will develop instead of vesicular emphysema The second is constant and is found in all normal lungs The third is found in all examples of hypertrophic emphysema

Patients with bronchiolar emphysema show essentially the same physical and laboratory findings as do those with vesicular emphysema The two are probably varieties of the same disease and should be classified as types of hypertrophic emphysema Muscular hypertrophy and fibrosis are outstanding features but the fundamental abnormality is emphysema

**Observations on Pathogenesis and Sequelae of Interstitial Inflammation and Fibrosis of Lungs** David M Spain[2] reviewed an extensive group of cases in which autopsy had proved interstitial pulmonary changes Interstitial pulmonary fibrosis unrelated to tuberculosis bronchiectasis or suppuration is evidently more common than in previous years

Several broad classifications are possible (1) forms related to a definite disease or specific cause such as berylliosis Boeck s sarcoid miliary tuberculosis and lipid pneumonia (2) types associated with some definite disease such as scleroderma lupus erythematosus and perhaps rheumatoid arthritis (3) changes secondary to basic disturbances in the lungs such as chronic pulmonary congestion or following hexamethonium therapy for hypertension (4) forms due to acute infection usually virus and (5) those without demonstrable etiology

Intra alveolar fibrin produced by various noxious agents often becomes plastered against the alveolar wall as a hyaline membrane This may be the initiating factor in cases which become interstitial fibrosis A relative lack of polymorphonuclear leukocytes has been postulated as the reason fibrinolysis is inadequate allowing the intra alveolar fibrin to remain as a stimulus and scaffold for fibroblastic proliferation

A similar mechanism may explain the interstitial fibrosis of the lungs in some patients who have rheumatoid arthritis

( ) J Mt S H p 24 1 50 1 57 N Dec 1957



F g 18 Ag nulocyt c pneumonia with s d able fib n ca e f rhe m to d rth t s t eated t el w th rt o e (C urte y of Spa n D M J Mt S ai H sp 4 1 50 1 57 No Dec 1957)

Most of these patients have received corticosteroids These steroids inhibit the usual inflammatory response may mask infections in the lung and have been responsible for agranulocytic forms of pneumonia (Fig 18) When such therapy is discontinued these predominantly fibrinous pneumonias may organize Thus the fibrosis reportedly associated with rheumatoid arthritis may be more closely related to therapy than to the underlying disease

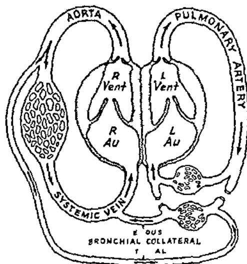
Fibrosis of the lung may lead to alveolar cell hyperplasia and ultimately to terminal bronchiolar (alveolar cell type) carcinoma

**Anatomic and Functional Studies of Lung Deprived of Pulmonary Arteries and Veins with Application in Therapy of Transposition of Great Vessels** are reported by Romeo A Vidone and Averill A Liebow[3] (Yale Univ ) The main trunk of the left pulmonary artery and the homolateral veins were tied in 10 dogs If the veins and artery to the lung were interrupted simultaneously there was orderly ingrowth of arterial and venous collaterals establishing connections with the corresponding pulmonary arteries and veins on the par

(3) Am J P th 33 539 571 May Ju e 1957

enchymal side Fistulous connections did not occur The transpleural collaterals must develop from capillaries in the granulation tissue of adhesions The venous collaterals developed at the same rate as the arterial

The vastly expanded bronchial arteries supply the lung by way of precapillary anastomoses with branches of the pul




F g 19 —Eff t of l g t g pulm n ry rte d v s f n l g tra po t on f g e t ls A t g yg t th l g p ated n t d d to r ght d d sy t m c rcu t Th l ng ece s d t t d blood f m tra pos d rta p ded b on h al rt rie d ft r o yg t g t r t rns t t ght heart pa d d b o h l ll t l Lobe ath th l g could be mila ly t t d (Court sy f V d R A a d Lebow A A. Am J P th 33 539 571 M y J 1957 )

monary arteries beyond the ligature which are still patent Enlarged bronchial veins drain the lung by augmented pre capillary connections with the pulmonary vein The original alveolar capillaries continue to be interposed between the remote arterial and venous collateral limbs therefore respiratory function can recover rapidly

When both pulmonary arteries and veins are ligated the collateral flow represents a large shunt of blood from the ao ta to the right side of the heart In transpo i ion of the great vessels the objective is to bring oxygenated blood into the aorta This cannot be accomplished merely by ligating the pulmonary veins of one lung because the pulmonary

arterial pressure is elevated in half such cases, sometimes *higher than the systemic arterial pressure* *Simultaneous ligation* of the pulmonary arteries and veins eliminates this danger With the development of collaterals an efficient autogenous oxygenator is present receiving desaturated blood from the aorta delivering it saturated to the right atrium and thus to the transposed systemic circuit (Fig 19) This operation has the advantage that the direction of flow is left to right in contrast to procedures which introduce a large interatrial defect or a connection between the pulmonary veins and right atrium in which blood can flow in either direction

**Formation of Bullae or Cystlike Cavities during Chemotherapy in Rabbits with Pulmonary Tuberculosis** Thin walled bullae developing during chemotherapy in the lungs of patients with pulmonary tuberculosis have been called giant or emphysematous bullae bullous cavities tuberculous cavities with bullous form cystlike cavities insufflated cavitation and thin walled cavities produced by chemical casectomy They appear commonly in areas of dense disease during administration of isoniazid William Steenken Jr and Emanual Wolinsky[4] (Saranac Lake N Y ) observed similar lesions in rabbits early in the course of effective chemotherapy for virulent bovine tubercle bacilli

Streptomycin isoniazid PAS with streptomycin or isoniazid isoniazid with streptomycin or PAS streptomycin isoniazid were effective in tuberculous lesions in 54 rabbits Bullae were formed in 61% of the rabbits regardless of the regimen used as long as it was effective A cystlike cavity was usually first seen 3 8 weeks after the start of chemotherapy A rounded thin walled radiolucent cavity suddenly appeared in an area previously occupied by shadows denoting a dense solid lesion They sometimes enlarged to occupy the greater part of the hemithorax and in several rupture caused spontaneous pneumothorax

At autopsy (Figs 20-22) air forced into the trachea inflated the bullae and pulmonary parenchyma Release of pressure on the trachea allowed the lung tissue to deflate but the air remained trapped in the bullae Caseous areas in the wall of each cyst projected into the lumen In rabbits that survived the acute stage the bullae soon lost their rounded con

(4) Am Rev T be c. 75 965 974 June 1957



F'g 0—La g r m v d t a t psy h wing th n walled b llae p jecting from p en hyma (C rte y f Stee ken W J and Wol n ky E Am R v I berc 75 965 974 June 1957)



F g 21—C t t on through b lla d t h Caseo foci d blood e sels w ll f b ll (Co rt y f St enk W J and Woli sky E. Am. Rev T berc. 75 965 974 J 1957)

tour shrank and filled with caseocalcific material ultimately becoming small calcified scars

The mechanism is unknown but a check valve obstruction must have been produced in the bronchus during the



Fig 22—U m gn fi d th secti th gh l g nd bull e (C rt sy f Steeken W J nd W l ky E Am R Tub c 75 965 974 J n 1957)

initial stages of healing due to inflammation and edema which later subsided The pneumonic lesions probably also softened during early treatment and when they were evacuated through the bronchi bullae could be formed ✓

► [These experimental observations provide a conclusive demonstration of the correctness of the postulate that bullous formations may result from a sequence of inflammatory and reparative processes associated with lung infections This study by Steenken and Wolinsky also reflects the growing clinical importance in pulmonary tuberculosis under chemotherapy of differentiating between the prognostic significance of such lesions and that of persistent tuberculous cavities formed by thick walled caseous granulation tissue (see Weiner and Boldowsky p 190 and Tchertkoff *et al* p 191) — Ed ]

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## PULMONARY FUNCTION

**Alveolar Capillary Block Syndrome** is characterized clim cally by hyperventilation dyspnea tachypnea cyanosis at first only on exercise but subsequently also at rest basal rales no w heezing or signs of endobronchial obstruction and late in the course of the disease by right heart failure Club

bing may or may not be present Chest x ray shows diffuse pulmonary infiltration

The diffusing capacity of the lung is reduced with uniform reduction in lung volume normal residual volume/total capacity ratio normal maximum breathing capacity normal distribution of inspired gases hyperventilation at rest anoxemia on exercise normal or decreased arterial carbon dioxide tension, elevated pulmonary artery pressure and often elevated right ventricular end diastolic pressure and reduced pulmonary compliance

The term alveolar capillary block implies the septum is involved by some process inflammatory granulomatous or neoplastic This is usually the case but Mortimer E Bader and Richard A Bader[5] (Mount Sinai Hosp New York) emphasize the point that functionally the surface for gas exchange is the total surface of ventilated alveoli perfused by pulmonary capillary blood Pathologic changes affect the membrane not only in thickness and physicochemical properties but also in surface area and pulmonary capillary flow The factors which influence the amount of oxygen diffused are the tension of gas proximal to the alveolar capillary mean tension distally time available for diffusion surface area and thickness of the membrane solubility of the gas physicochemical properties of the membranes and finally blood flow in the lung

At rest the diffusing capacity of the lung for oxygen is normally greater than 15 cc /mm pressure difference/minute On exercise it increases about fourfold largely because of increase in number of pulmonary capillaries which become patent and increase in the surface area by dilatation of the capillary bed as a whole

Maximum diffusing capacity decreases with age In pathologic states a decrease is demonstrable sometimes only with exercise due to decrease in the number of capillaries and restriction in dilatability Thus diffusing capacity may be reduced not only by a block at the diffusing surface but by reduction in total surface area or reduction in blood flow to the lung The diseases associated with alveolar capillary block are Boeck s sarcoid berylliosis scleroderma of the lung acute miliary tuberculosis lymphangitic carcinosis mitral stenosis histiocytosis of the lung interstitial fibrosis

(5) Am J M d 24 493-496 Ap 1 1958

or granulomatosis of unknown etiology asbestosis eo ino philic pneumonia and po tradiation fibrosis

If emphysema is not present ventilation is not signifi cantly disturbed and secondary infection is less common Bronchodilators are of no help for the respiratory distress and antibiotics are infrequently required Since the primary defect is usually interstitial pulmonary compliance is de creased and the mechanical work of breathing is increased Unless the cause is tuberculosis the principal therapy is adrenal steroids which has resulted in limited success

Oxygen therapy in this syndrome is not dangerous, in con trast to emphysema and other diseases of alveolar hypo ventilation since arterial carbon dioxide tension is normal or even reduced Because carbon dioxide is easily diffusible it readily passes across even markedly diseased membranes

Since the right heart failure in this syndrome is due pri marily to restriction of the pulmonary vascular bed by organ ic change and to a lesser extent to the anoxemia reversing the hypoxemia will only partially and temporarily improve the cor pulmonale unless steroid therapy effects improve ment in the constrictive disease of the pulmonary vascular bed

► [The syndrome of alveolar capillary block is a relatively new one hav ing been first defined in 1951 by Cournand and his co workers This editorial summary by Bader and Bader points out the value of the concept particularly in relation to the diagnosis and management of the diseases which have these functional features in common—Ed]

**Measurement of Pulmonary Diffusing Capacity in Pres ence of Lung Disease** If pulmonary diffusing capacity is de fined as the sum of the diffusing capacity of each alveolus then it cannot be exactly measured if diffusion within the lung varies All contemporary methods estimate the rate of gas uptake either over a timed interval of breath holding or during a steady state experiment dividing this by a calcu lated mean pressure of the gas No over all measurement made this way can represent the correct over all diffusing capacity of the lungs Each of the methods used carbon mon oxide single breath steady state Filley end tidal sampling radiocarbon carbon monoxide and the oxygen methods all have limitations and uncertainties

D V Bates[6] (McGill Univ ) estimated the pulmonary dif fusing capacity in 151 patients and found the end tidal sam

(6) J Clin Invest 3 591 605 Ap 1 1958

pling method of measuring mean alveolar CO concentration to be valid During exercise the Dco calculated from such samples corresponds well to that estimated from the Bohr equation to compute the mean alveolar CO concentration With exercise the rate of CO uptake is a sensitive measure

COMPARISON BETWEEN RESULTS OBTAINED BY DIFFERENT AUTHORS OF MEASUREMENTS OF PULMONARY DIFFUSING CAPACITY IN 3 DISEASES

| Disease | State | No. studied | Method* | Lowest† | | hest† | | reference |
|---|---|---|---|---|---|---|---|---|
| | | | | $D_{O_2}$ | Dco | $D_{O_2}$ | Dco | |
| Chronic respiratory disease em yema | | | | | | | | |
| | Rest | 16 | ss$D_{O_2}$ | 0 | 3.25 | 14 0 | 1 0 | (1) |
| | Rest | 57 | ssDco | .3 | 3 5 | 21 0 | 1 0 | ( ) |
| | Res | | He-CO S B | 4.3 | 3 5 | 43 2 | 35 2 | ( ) |
| | Rest | 35 | ssDco | 5 0 | 4 1 | 1 .8 | 12 0 | (2 ) |
| Chronic bronchi and emphysema | | | | | | | | |
| | Res | 12 | C*O | 13.5 | 1 0 | 3 | 25 0 | (10) |
| Chronic airway d sease | | | | | | | | |
| | Exercise | 27 | ss$D_{O_2}$ | 1 0 | 8 | 5 0 | 36 6 | (2) |
| Emphysema | | | | | | | | |
| | Exercise | 15 | ssDco | 5.9 | 4 8 | 7.2 | 4 0 | (33) |
| Pulmonary fibrosis (d ffuse intersti ial fibrosis) | | | | | | | | |
| | Rest | | ss$D_{O_2}$ | 0 | 3.25 | 0 | 8 1 | (1) |
| | Rest | 2 | ssDco (F) | 4.8 | 3 90 | 8 6 | 0 | ( ) |
| | Res | 2 | He-CO S B | 8 7 | 7 | .5 | 10 2 | ( ) |
| | Exercise | | ssDco (F) | 1 .5 | 2.6 | 2 | 8 | (6) |
| | Exercise | 4 | ssDco | 5 6 | 4 6 | 1 .2 | 1 8 | (T ble I) |
| Sarcoidos | | | | | | | | |
| | Rest | 2 | ss$D_{O_2}$ | 7 0 | 5 7 | 7 0 | 5 7 | (35) |
| | Res | 8 | ss$D_{O_2}$ | | .2 | 23 | 8 7 | (36) |
| | es | 3 | ss$D_{O_2}$ | 5 | 3 | | | (27) |
| | Rest | 1 | He-CO S B | 4 | 4 0 | | 0 | ( ) |
| | Res | 7 | ss$D_{O_2}$ | 14 0 | 11 4 | 18 0 | 1 6 | ( ) |
| | Rest | 6 | ssDco (F) | 7.2 | 5 9 | 6 1 | 13 1 | ( ) |
| | Res | 15 | ssDco | 5 0 | | 4 | 15 8 | (20) |
| | Exercise | 3 | ss$D_{O_2}$ | | | 23 0 | 7 | (27) |
| | Exercise | | ssDco (F) | | | .5 | | ( ) |
| | Exercise | 15 | ssDco | 5 | 5 3 | 1 | 15 | ( 0) |

D stead tat ygen m thod H CO S B m d fi d K h gl b th meth d D (F) t dy t CO tech g t 1 pCO D te d t t CO t h as m g l f p t ry dead p Dc t dy t t CO tech nic g m d d t d l CO on t t on C O d oact CO method
†Act l m m t h wn m n typ d mp t d eq l t D D in talic

ment and can detect abnormal pulmonary diffusion but not at rest The steady tate Dco measured during exercise in patients with the Hamman and Rich syndrome of diffuse pulmonary fibrosis cannot be correctly converted to the Do_ by the usual conversion factor The end tidal sampling technic with carbon monoxide is adequate to estimate the relative normality o lung parenchyma in patients with asthma and emphysema

Despite the many uncertainties in measuring pulmonary

diffusing capacity by any technic the general form of reported results in 3 different lung diseases (table) suggests that all methods give about the same results This probably indicates that all available methods are being influenced in the same direction by similar causes of error

The steady state carbon monoxide technic is the simplest to use Since the normal subject increases pulmonary diffusing capacity considerably on exercise the difference between normal and abnormal lungs is greatly accentuated by exercise and all patients should be studied during exercise if possible This reduces the method errors since the tidal volume is increased and discriminates more sharply between normal and abnormal

Physical Properties of Lungs in Chronic Cor Pulmonale J D S Hammond[7] (Univ of Sheffield) studied the compliance and nonelastic resistance of the lungs in 5 normal subjects and 31 patients with chronic bronchitis and emphysema of whom 17 had chronic cor pulmonale Of the latter 12 were studied during an attack of heart failure and after recovery Air flow tidal volume and intrathoracic pressure were recorded simultaneously Intraesophageal pressure was measured by the long balloon and polythene tube the balloon in the lower third of the esophagus The upper end of the tube was connected to a diaphragm gauge which had a mechanoelectronic transducer Air flow was recorded with a Lilly pneumotachygraph Volume changes were recorded directly by electric integration of the signal from the pneumotachygraph using a simple condenser and resistance circuit

Pulmonary compliance the reciprocal of the coefficient of elastic resistance was calculated from the intraesophageal pressure and volume tracings by relating the tidal volume to the pressure difference at the points of no flow at the beginning and end of inspiration Nonelastic resistance was calculated at the points at which the volume of inspired and expired air was half the tidal volume for the breath The pressure required to overcome elastic resistance was calculated from the pressure volume relation assumed to be linear and substracted from the intraesophageal pressure at the points mentioned to give the pressure required to overcome nonelastic resistance Compliance was expressed as volume change/unit pressure in liters/centimeter of water and the

(7) Clin S 16 431-487 1957

nonelastic resistance as the pressure in centimeters of water required to produce a rate of air flow of 1 L/second

Several factors may produce the marked decrease in compliance observed in patients with emphysema during heart failure Respiratory infections commonly precipitate congestive failure in many forms of heart disease including chronic cor pulmonale All patients studied had such an infection at the time of failure The acute inflammation probably added to the pulmonary rigidity and contributed to the reduction in compliance In acute pneumonia the increase in lung rigidity is greater than can be accounted for by changes in the consolidated areas and in part is due to congestion of both lungs The infection also causes increased bronchial secretion and obstruction further increasing the nonelastic resistance Most patients breathed more rapidly during heart failure than after recovery and the association of a higher respiratory frequency and an increase in nonelastic resistance must thus have reduced compliance Pulmonary hypertension in patients with emphysema and heart failure might also decrease the distensibility but this is not likely Increased anoxia by increasing capillary permeability might cause pulmonary edema and further reduce compliance

Recovery from heart failure in patients with emphysema is usually followed by a decrease in nonelastic resistance and increase in compliance However of 15 patients studied only 5 had pulmonary compliance after recovery from failure which was within the range found in uncomplicated emphysema and these were the only patients who subsequently did not require diuretics or salt restriction to prevent recurrent failure The patients with chronic cor pulmonale who had a poor prognosis were those who had had many episodes of heart failure in whom permanent changes such as persistent edema and congestion might have caused a reduction in pulmonary compliance

**Syndrome of Alveolar Hypoventilation and Diminished Sensitivity of Respiratory Center** is described by Tor Richter John R West and Alfred P Fishman[8] (Columbia Univ) *Normally an increase of only a few millimeters of mercury in partial pressure of arterial carbon dioxide will double or triple minute and alveolar ventilation* In various diseases characterized by carbon dioxide retention this sensitivity is

(8) N w E gl nd J M d 56 1165 1170 J 20 1957

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(7) Cl Sc 16 481-489 1957

**Pulmonary Function in Obesity** may be disturbed some times accompanied by sleepiness and periodic breathing without primary disturbances in the lungs heart blood or metabolism according to reports in the literature H Isenschmid A Buhlmann and F Schaub[9] (Univ of Zurich) report *blood gas analyses and spirometric studies in 12 patients* weighing over 100 kg (220 lb) in whom other causes of pulmonary dysfunction (lung and bronchial diseases left sided cardiac insufficiency Cushing s disease polycythemia vera etc) could be excluded

As to oxygen saturation and carbon dioxide tension the patients could be divided into three groups In 2 men and 2 women (average weight 112 5 kg) blood oxygen was normal carbon dioxide normal or slightly decreased and pulmonary function essentially normal One man and 1 woman (average weight 124 5 kg) had slight hypoxemia normal carbon dioxide and partial pulmonary insufficiency In 6 patients (5 *men*) *whose average weight* was 143 kg tests showed decreased blood oxygen increased carbon dioxide respiratory acidosis and slight but definite insufficiency

These findings demonstrate a definite relation between degree of functional disturbance and body weight There was no correlation with age all had been grossly overweight since youth Erythrocyte counts and hemoglobin were slightly over the usual average but within normal range and were the same in those with and without pulmonary insufficiency

Spirometry showed normal average value for total and vital capacity but percentile ratio of functional residual capacity to total capacity was decreased to 37 7% (normal 43%) Similar findings have been reported in ascites pneumoperitoneum and during the last half of pregnancy The breathing rate was decreased in all patients Specific ventilation (relation of minute volume to oxygen consumption per minute) averaged 26 8 within normal range In 3 patients the blood gases tended to become normal in the upright position and with slight exertion The mechanics of breathing studied in 1 case were normal cardiac catheterization in the same patient showed pulmonary hypertension After loss of 15 kg this patient still showed slight hypoxemia but carbon dioxide was practically normal

(9) H l et m d ta 4 8 90 J ly 1957

lost but the specific mechanism that limits ventilatory response may be difficult to isolate since an unresponsive respiratory center bronchial obstruction impaired mechanical efficiency of the chest bellows or all three may be involved A case is reported in which a distinction seemed feasible The alveolar hypoventilation was secondary to a damaged respiratory center whereas the lungs and chest bellows were normal

Man 37 had cyanotic lips while asleep since childhood Intermittent cyanosis and weakness had occurred since age 34 During an acute febrile illness he had severe cyanosis and peripheral edema responding to oxygen phlebotomy digitalis and antibiotics Angiocardiography on two occasions was normal Physical examination revealed a small well developed thin alert man in no distress who had faint cyanosis of the lips and nail beds The hematocrit was 54 4% The ECG showed right axis deviation

Pulmonary function tests showed slightly reduced vital capacity increased residual volume and resulting normal total lung capacity There was no evidence of air trapping or prolonged expiration Alveolar ventilation was considerably reduced and the ratio of dead space to tidal volume increased Arterial blood oxygen saturation was 70% carbon dioxide content 95 ml /100 ml and pH 7 28 Minute ventilation barely doubled during exercise and though cyanosis increased markedly the patient had no distress and no dyspnea Arterial blood carbon dioxide increased still further pH fell to 7 24 and oxygen saturation fell to 51% During passive hyperventilation with ambient air using intermittent positive pressure breathing apparatus the hemoglobin became fully saturated and respiratory alkalosis replaced the acidosis

The marked degree of carbon dioxide retention the failure to increase minute ventilation normally during exercise and the diminished ventilatory response to inspired carbon dioxide all indicated alveolar hypoventilation and impaired sensitivity of the respiratory center to normal chemical stimuli The syndrome is limited ventilatory response imposed by an insensitive respiratory center rather than by obstructive pulmonary disease or malfunctioning chest bellows

► [This type of respiratory center disease has similarities with the so-called pickwickian syndrome of alveolar hypoventilation associated with extreme obesity but is distinguished by the absence of a mechanical factor (i e the impaired function of the chest bellows)

In the following paper from Rossier s clinic the authors point out that the hypoventilation syndrome in obesity may not be caused simply by the mechanical inhibition of respiration and by inference that the somnolence which is so prominent a feature in the pickwickian syndrome is not merely a consequence of the ventilatory disturbance Indeed these authors regard the tendency to somnolence and to periodic breathing as evidences of a general regulatory disturbance of motor functions in obesity —Ed ]

insufficiency improved in the present patients with weight loss Specific cause of the respiratory insufficiency and somnolence thus remains obscure

Lack of erythrocytosis in these cases may seem surprising but it is emphasized that pulmonary insufficiency was mild in all Further the functional disturbance disappeared or decreased during activity for a considerable part of each day thus the stimulus toward increased erythropoiesis was slight and insufficient to influence the blood picture

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## EMPHYSEMA

**Prolonged Observations of Patients with Cor Pulmonale And Bullous Emphysema after Surgical Resection** Martin J Fitzpatrick C Frederick Kittle T K Lin and Diane T Brukardt[1] (Univ of Kansas) surgically ablated large bullae in 6 patients and followed them for at least 1 year All had histories of chronic cough for many years with gradually increasing exertional dyspnea punctuated by frequent chest colds The men had to stop work because of progressive pulmonary insufficiency and 3 were in intractable cardiopulmonary failure at the time of surgery A seventh man 69 in severe failure died 36 hours after operation and was not included

All 6 survivors were subjectively improved in the early months after surgery 3 men were able to return to gainful work 1 developed postoperative empyema requiring thoracoplasty and 1 died of cerebral hemorrhage 16 months later Ventilatory function did not change appreciably (Fig 24) Pulmonary arterial pressure decreased immediately in all but later returned to preoperative values in some the most striking reduction was noted in those who had the most severe congestive heart failure and the highest pulmonary arterial pressure preoperatively

Pulmonary emphysema a predominantly degenerative pulmonary disease of aging men is most frequently associated with chronic bronchitis Over many years pulmonary reserve gradually and progressively decreases The resulting abnormal lung volumes obstruction to air flow increased

(1) Am R T b r 77 387 399 M ch 1958

Alveolar hypoventilation hypoxemia and hypercapnia observed in 6 patients seemed to be related to increased mechanical difficulty in breathing since they improved in the upright position with light exertion and after weight loss Mechanical factors however are probably not the sole cause since somnolence and involuntary falling asleep were promi

F g 23 —Sp g m h ont l po t n P t ent f ll l p d g p metry b e th g be me per od w th p se t 40 econds aft b th ng p occa o ally d p p t d compa y g s d ea f b th l m occur d (C urtesy f l hm d H t l H l t m d ta 24 8 90 J ly 1957)

nent and constituted the patients chief complaints In 3 of 6 with general insufficiency periodic breathing with pauses as long as 40 seconds (Fig 23) was observed while they were sleeping during spirometric tests Of the 6 without hypoventilation only 2 displayed a suggestion of periodic breathing with pauses not exceeding a few seconds Tendency to fall asleep even in the 3 most evere cases with intermittent breathing occurred only when the patients were lying or sitting not during work or accidentally Although patients with true narcolepsy are often obese sleepine s does not improve with dieting whereas both somnolence and respiratory

insufficiency improved in the present patients with weight loss Specific cause of the respiratory insufficiency and somnolence thus remains obscure

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(1) Am Rev T bc 77 387 399 M h 1958

Maximum Breathing Capacity % Predicted Normal

NORMAL

MONTHS FOLLOWING OPERATION

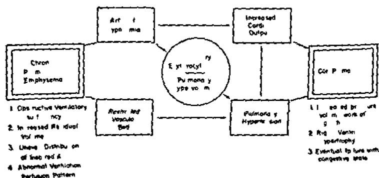
Mean Pulmonary Artery Pressure Mm Hg

NORMAL

MONTHS FOLLOWING OPERATION

Fig 24 –Ch ng n c rd pulm ty fun t n aft pe t (Co rtesy of F t pat ck M J t l Am Re Tuberc 77 387 399 March 1958)

## Factors Contributing to Development of Cor Pulmonale



work of breathing and abnormal ventilation perfusion relation are often associated with gradual anatomic reduction in capacity of the normal voluminous capillary bed and fixed pulmonary hypertension (table) Intercurrent bronchial infections with further hypoxemia accentuate these abnormalities and contribute to the ultimate cardiac hypertrophy dilatation and failure of the right heart

**Anoxia in Emphysema Relief by Oxygen** In patients with emphysema a respiratory infection may produce anoxia Administration of oxygen to relieve the anoxia may precipitate carbon dioxide narcosis Thomas Simpson (Enfield England) investigated the effects of anoxia on the central nervous cardiovascular hemopoietic hepatic and renal systems The organic changes were profound and indicated anoxia should be relieved whenever possible

CASE 1—Man 56 had chest trouble for 7 years After a bad chest cold he had become cyanotic irrational and in and out of stupor In lucid moments he realized he had been irrational Examination showed loss of cardiac dulness hyperresonance and poor air entry Albuminuria was present He was given penicillin and placed in an oxygen tent but quickly went into coma recovering when removed At the end of 24 hours of intermittent oxygen therapy he refused further treatment because he was suspicious and paranoid He was transferred to a psychiatric hospital and after 3 days of intermittent coma and cyanosis he died Autopsy revealed bullous emphysema and acute suppurative inflammation of the entire bronchial tree occlusion of most of the bronchi by ropy mucopurulent discharge hypertrophy of the right ventricle sclerosis and atheroma of the pulmonary artery and intense cerebral congestion with hemorrhages in the gray and the white matter

CASE 2—Man 37 had winter bronchitis for 7 years and was unable to do even inside work because of increasing dyspnea He was admitted because of a respiratory infection Oxygen saturation was 39% but clinical examination of the lungs was unremarkable A chest x ray showed increased translucence of the lungs with a large bulla in the left midzone compressing the upper lobe Oxygen by nasal catheter at low rates of flow relieved dyspnea but within 3 months the patient was using oxygen continuously throughout the day at an increased rate of flow and occasionally at night Within the next 2 months he was taking 8 L/min day and night This was considered unnecessary and oxygen discontinued Within minutes the patient s condition became acute and his color black Oxygen saturation was 38% Thereafter he had oxygen continuously by nasal catheter 8 L/min (Fig 25) During the whole period of oxygen therapy his mental state was clear After a year of therapy his condition suddenly and unexpectedly deteriorated and he died Autopsy was refused

(2) L et 2 105 113 J ly 20 1957

Maximum Breathing Capacity / Predicted Normal

NORMAL

100, 80, 60, 40, 20, 0

6, 12, 18, 24

MONTHS FOLLOWING OPERATION

Mean Pulmonary Artery Pressure Mm Hg

60, 45, 30, 15, 0

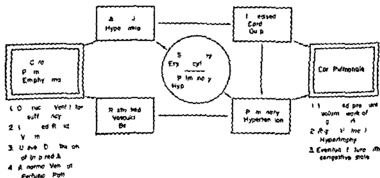
NORMAL

6, 12, 18, 24

MONTHS FOLLOWING OPERATION

Fig. 24.—Changes in ... d pulmonary function after operation. (Courtesy of Fitzpatrick, M. J., et al.: Am. Rev. Tuberc. 77:387-399, March 1958.)

*Factors Contributing to Development of Cor Pulmonale*



well known Severe anoxia can cause irreversible changes in most human organs and with exercise of due caution it should be relieved whenever possible The ill effects of carbon dioxide narcosis may be reversible those of unrelieved anoxia are not

► [Since the recognition that oxygen administration in respiratory acidosis may precipitate carbon dioxide narcosis the emphasis has been almost entirely on the importance of avoiding this danger in the treatment of emphysema. The equal or greater importance of relieving anoxia when this is severe by the *proper* administration of oxygen is illustrated in this careful study which merits reading in the original —Ed ]

**Effects of Aminophylline and Diamox® Alone and Together on Respiration and Acid Base Balance and on Respiratory Response to Carbon Dioxide in Pulmonary Emphysema.** Morton Galdston and Jack Geller[3] (New York Univ ) studied the effect of intravenous aminophylline 0 5 Gm and

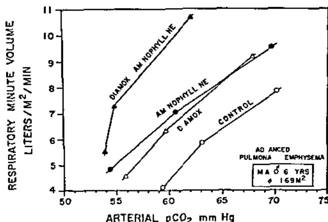


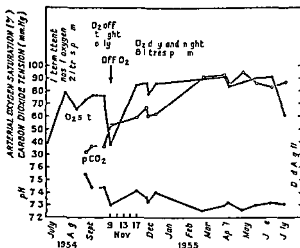

Fig 26—Effect f m phyll d D m ® l d t geth on esp rat ry po t d rteri l P C rv d w th gh m f l Low t t f h rve p t b ry t d g b l t on f 100% xyg ext d ing h lat f m xt f 2 54% ca bo d oxid d 93 46% xygen d high st n t d g h lat f m t f 4 91% b d d d 95 09% o yg (Courtesy f G ld ton M d G ll J Am J Med 23 183 196 A gu t 19 7 )

orally administered Diamox® every 12 hours alone and with aminophylline on the respiratory response of 4 patients with moderate and 2 with advanced emphysema to arterial Pco (H ) ion stimulation induced by inhaling carbon dioxide and oxygen mixtures

The patients with moderate emphysema responded nor

(3) Am J M d 23 183 196 A g t 1957

When the patient with emphysema has a chest infection the resulting anoxia stimulates the respiratory center unless it is too severe in which case it depresses the center If oxy gen is given the anoxic drive to increased respiration is removed the minute volume of respiration decreases and carbon dioxide accumulates in the blood If carbon dioxide accumulates rapidly the pH decreased considerably If the




F g 25 —Se 1 bl od g ly s n Ca 2 (Court y f S mp T Lan et 2 105 113 July 20 1957 )

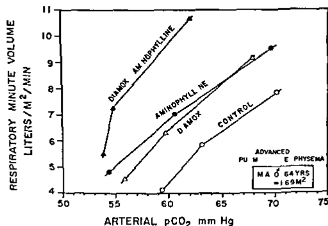
acidemia is more important than the hypercapnia in produc ing the ill effect of oxygen therapy administration of gradu ally increasing concentrations would cause less mental disturbance because the increase of carbon dioxide in the arterial blood and the lowering of pH would be gradual and compensation could occur Severe hypercapnia is compatible with a normal mental state provided the pH is not suddenly or greatly decreased (Fig 25) Even if coma does follow oxygen therapy it is not necessarily fatal Another danger of oxygen therapy addiction to oxygen may occur

Severe or unrelieved anoxia induces irreversible and his tologically demonstrable changes in the liver Renal function is impaired Spontaneous bleeding is common probably due to damaged capillaries The effects of anoxia on the central nervous cardiac respiratory and hemopoietic systems are

well known Severe anoxia can cause irreversible changes in most human organs and with exercise of due caution it should be relieved whenever possible The ill effects of car bon dioxide narcosis may be reversible those of unrelieved anoxia are not

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F g 6 —Effect f am phyll d D m ® lon and t geth on p ratory pon t cr d rt l Pc C d w th gh m f l Low t po t I ea h p ent b rv t d g h l t on f 100% xygen next d ri g h lat on f m t f 2 54% a bo dioxid d 93 46% xygen d h gh t po t d g h l t on f m t f 4 91% ca bon d x d d 95 09% g (C rt y f G ld to M d G ll J Am J M d 23 183 196 A gust 1957 )

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(3) Am J M d 23 183 196 A g t 1957

mally sensitivity was decreased in those with advanced disease No patient showed a significant increase in sensitivity with the drugs even when the drugs caused significant reduction in arterial Pco plasma $BHCO_3$ and arterial pH In 1 patient the respiratory response increased approximately two three and fourfold with respectively Diamox® aminophylline and both concurrently (Fig 26) Of the 2 patients with advanced emphysema 1 exhibited a significant increase following aminophylline neither did with Diamox® and both responded to combined Diamox® and aminophylline by more than the additive response of each separately

That the two drugs together increase the ventilatory response to arterial Pco (H ) ion stimulus suggests they may be effective in preventing and in treating carbon dioxide retention and respiratory depression in some of these patients during inhalation of oxygen enriched air Continued administration may delay or even prevent the development of abnormal regulation of respiration in patients with chronic pulmonary emphysema

The immediate effects of aminophylline Diamox® and both together on minute ventilation respiratory gas exchange oxygen uptake alveolar Po acid base balance and oxygen saturation of arterial blood hemoglobin maximum breathing capacity and vital capacity were studied The changes were most marked when the two drugs were administered together After 45 minutes observation moderate ventilatory stimulation was generally present alveolar Po and arterial blood hemoglobin oxygen saturation increased arterial Pco at or several millimeters of mercury below control level and arterial pH reflected the trend in arterial Pco, since plasma $BHCO_3$ level did not change In some the reduced arterial Pco following aminophylline compensated partially the metabolic acidosis induced by Diamox®

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## PNEUMOCONIOSIS AND OTHER INHALATION DISEASES

**Breathless Coal Workers as Seen at Golden Clinic** Elkins W Va present a syndrome identical with or similar to coal workers pneumoconiosis in Great Britain according to J F

Martin Jr[4] The classification of chest x rays established by the Pneumoconiosis Research Unit of the Medical Research Council can be applied to the chest x rays of American miners

Routine physical and laboratory examinations reveal only a restriction in respiratory excursion of the chest occasionally right ventricular strain but markedly abnormal chest films

MAXIMAL BREATHING CAPACITY FOUND IN VARIOUS CATEGORIES OF COAL MINERS PNEUMOCONIOSIS

| X Ray C tegory | MBC % f Estimated No mal N of Cases | | | | Tot l C ses |
|---|---|---|---|---|---|
| | <35% | 35% 54% | 55% 9% | 80% + | |
| 0 | 14 | 4 | 10 | 1 | 29 |
| 1 | 2 | 11 | 10 | 15 | 38 |
| 2 | 3 | 14 | 9 | 24 | 50 |
| 3 | 1 | 6 | 6 | 5 | 18 |
| PMF | 4 | 3 | 12 | 9 | 28 |
| Total | 24 | 38 | 47 | 54 | 163 |

X ray t g th e t bl h d by the P moc R h U t

and decreasing maximal breathing and vital capacity Respiratory function cannot be estimated by inspection of a chest x ray All degrees of disability occur in all categories of x ray change as shown by the values for 163 miners (table) Respiratory function is sometimes impaired in miners with little or no detectable x ray change and some with marked x ray changes have normal function

Pneumoconiosis or pulmonary emphysema cannot be cured but can be improved Patients are urged to ambulate nonrespiratory disorders are treated antibiotics are used frequently if yellow sputum elevated sedimentation rate or low grade fever indicate infection 10 drops potassium iodide 3 times daily is given as an expectorant and bronchial dilators by mouth or parenterally are given occasionally Isoproterenol given by nebulization with intermittent positive pressure breathing seems to give most relief Most patients so treated show definite improvement in maximal breathing capacity

Man 79 had mined underground sin e age 16 hand loading coal He had moderate exertional dyspnea slight wheezing and moderate cough productive of variable amounts of sputum Blood pressure was 200/90 he had marked restriction of movement of the chest and a few

(4) A M A A h I d t H lth 15 494 498 J 1957

mally sensitivity was decreased in those with advanced disease No patient showed a significant increase in sensitivity with the drugs even when the drugs caused significant reduction in arterial Pco plasma $BHCO_3$ and arterial pH In 1 patient the respiratory response increased approximately two three and fourfold with respectively Diamox® aminophylline and both concurrently (Fig 26) Of the 2 patients with advanced emphysema 1 exhibited a significant increase following aminophylline neither did with Diamox® and both responded to combined Diamox® and aminophylline by more than the additive response of each separately

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**Breathless Coal Workers as Seen at Golden Clinic** Elkins W Va present a syndrome identical with or similar to coal workers pneumoconiosis in Great Britain according to J E

underground and 2 of these became delirious and lost consciousness Bilateral pleural effusions pericarditis and swollen hands developed in 1 pleural and pericardial effusions in 1 and acute polyarthritis followed by progressive skin changes in 1 Five of 6 with gradual onset had productive cough exertional dyspnea and bronchitis for several years followed by gradual development of skin changes

Pulmonary symptoms mainly productive cough dyspnea and chest pain occurred in all preceding skin changes in 10 and simultaneously with skin changes in 7 Sputum varied from small amounts of mucus to several ounces of purulent sputum daily Blood streaking was noted in 2 All showed exertional dyspnea and 9 showed nocturnal dyspnea

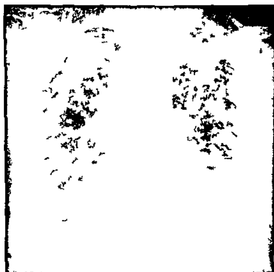
Chest movement was restricted Widespread bilateral rhonchi were noted in 12 The most frequent sign was coarse bilateral basal rales In 2 loud friction rubs were noted in the axillae Effort tolerance was reduced in 10 of 15 patients in whom it was measured In 2 of 3 in whom pulmonary function was measured all divisions of pulmonary volume were reduced and gas mixing was delayed but arterial oxygen saturation did not decrease with exercise

The roentgen changes of pulmonary scleroderma and of silicosis may show a reticular lung pattern or mottling In pulmonary scleroderma abnormal markings are mainly in the lower zones and cystic changes may be seen Only 5 patients had demonstrable changes in esophageal motility and these were mild

**Chronic Pulmonary Insufficiency Secondary to Silo Filler s Disease** A recent report emphasized that chronic pulmonary disease due to inhalation of silage fumes might be recognized in the future Gilbert M P Leib W N Davis Trave Brown and Mark McQuiggan[6] (Wayne County Gen l Hosp Eloise Mich ) report a case

Man 28 had a smothering sensation and headaches Four days earlier he had chills and fever and a cough producing whitish material Three years earlier he worked in a silo that had been filled the previous day with straight corn silage On opening the door he immediately noticed intense heat the eyes and nose burned and he choked That afternoon he felt smothered nauseated and feverish and for the next week had malaise weakness headache chest pain fever anorexia chilliness dyspnea on slightest exertion and cough productive of white sputum Chest x ray was said to be negative He was acutely ill

(6) Am J Med 24 471-474 M h 1958



F g 27—Ch t x ay of m ged 79 h wi g m s glom rates both upp lobes d g e l ed d lat (Court y f Ma t n J E. J A M A A h I du t H alth 15 494 498 J 1957 )

expiratory wheezes Chest x rays showed massive conglomerates in both upper lobes with generalized nodulation (Fig 27) The tuberculin test was strongly positive but many examinations and sputum cultures showed no bacilli Maximal breathing capacity was 30% of estimated normal vital capacity 1 2 L and 3 second vital capacity 100%

**Scleroderma in Gold Miners on the Witwatersrand with Particular Reference to Pulmonary Manifestations** L D Erasmus[5] (Univ of Pretoria) observed 17 cases for 18 months Most patients had clinical or radiologic evidence of pulmonary involvement and several had sudden almost explosive onset All but 1 a Bantu were European underground miners Age at onset of symptoms was 27 52 Most patients had had scleroderma for several months or years and the skin changes were diagnostic No good statistics are available on incidence of scleroderma in the general population but increased incidence among gold miners seems greater than can be accounted for by chance

The 10 patients with sudden acute onset each had severe chest pain of pleuritic type Three collapsed while working

(5) South Afri an J Lab & Cl Med 3 209 31 Sept mb r 1957

ifornia Los Angeles) report on 2 patients in whom diagnosis of calcified grass head in the right lower lobe was confirmed by surgery

Man 25 had hemoptysis At age 11 he aspirated a piece of foxtail grass which was followed by pneumonia and lung abscess Hemoptysis recurred at age 17 and 21 At age 24 he showed chronic cough with about 30 cc yellow sputum daily persistent hemoptysis and weight loss Admission chest x ray showed a calcified panicle in the right lower lobe (Fig 28) Bronchograms revealed extensive bronchiectasis Thoracotomy disclosed obliterated right pleural space and



Fig 28—Calcified panicle po t rio basal segment of right lowe lobe (Cou t sy of Hay D M et al D Chest 33 8-42 Jan ry 1958)

basilar bronchiectasis The resected segment contained a panicle 6 cm long dilated bronchi thickened pleura and chronic pneumonia The postoperative course was uncomplicated

Aspirated panicles rapidly move out of the range of effective endoscopy Forward motion is the result of constant to and fro respiratory motion of the tracheobronchial system passively moving the panicle Backward motion is prevented by the barbs In the preantibiotic era the usual course was rapid pa age through the thoracic wall with accompanying acute febrile illness or death due to pulmonary infection Antibiotic therapy enables survival of the initial acute infection Tolerance to the foreign body develops and the vegetable matter calcifies producing a cast of the original grass head Hemoptysis and bronchiectasis are characteristic

for 3 weeks and thereafter could not resume farm work because of dyspnea on slight exertion

On hospitalization he had moderate respiratory distress with slight peripheral cyanosis He had inspiratory and expiratory moist rales and scattered expiratory wheezes Chest film showed accentuated bronchovascular markings in the upper portions of both lung fields Pulmonary function tests (table) showed increased residual volume decreased maximal breathing capacity and slowing of the timed vital capacity characteristic of obstructive emphysema The low value for

SUMMARY OF FINDINGS

| STUDIES | PATIENT | NORMAL |
|---|---|---|
| Lung volumes | | |
| Vital capacity | 2 130 cc BTPS | 4 030 cc BTPS |
| Residual volume | 3 305 cc BTPS | 1 454 cc BTPS |
| Distribution of ventilation | | |
| Nitrogen rise over 500 cc of expiration | 3 8% | Less than 1 5% |
| Diffusion (CO method) | | |
| Steady state | 16 9 ml /mm Hg/min | 13 20 ml /mm Hg/min |
| Single breath | 29 0 ml /mm Hg /min | 17-40 ml /mm Hg/min |
| Mechanics of breathing | | |
| Compliance of lungs | 0 062 L /cm H O | 0 200 L /cm H O |
| Maximum breathing capacity | 47 2 L /min | 124 L /min |
| Timed vital capacity | | |
| 1 second | 64 7% | 83% |
| 3 seconds | 90 5% | 100% |
| Arterial blood gases | | |
| Arterial $O_2$ saturation | 97 4% | 96% |
| Pco | 30 1 mm Hg | 40 mm Hg |

pulmonary compliance may be attributed to decreased elasticity of the lungs though it may be related to the rapid breathing

This probably is the first reported case in which chronic pulmonary disease followed exposure to silage gas (acute toxicity from exposure to the oxides of nitrogen primarily nitrogen dioxide) The result is diffuse obstructive bronchiolar disease Farmers should be cautioned when in or about a recently filled silo even when no gas is apparent

Expectorants bronchodilators given with intermittent positive pressure and antimicrobials probably were of some benefit in this patient but the residual impairment in pulmonary function was severe and for the most part irreversible

—Radiopaque Grass Heads in Lung Daniel M Hays Gertrude T Huberty and Bernard J O Loughlin[7] (Univ of Cal

(7) Di Ch t 33 38-4 J ary 1958

active isotopes chiefly iodine and ruthenium tetraoxide and the dustlike effluvium of some 50 radioisotopes

During the chemical processing of spent fuel rods or liquid fuels fission products may get into the lungs The process is designed to operate by remote control and pulmonary haz ard is ordinarily negligible In a few instances the system has leaked or the stack has become overloaded Of most con cern are $Pu^{39}$ $Ru^{106}$ $I^{131}$ $Cs^{137}$ $Sr^{90}$ $Ba^{140}$ and perhaps tritium or $H^3$ which enter the respiratory tract as gases fine dusts or aerosols in other emitted vapors Containment and disposal of radioactive wastes should create no problem for the lung unless a container leaks or is broken The chronic effects of penetrating gamma or x radiation on the lung are fibrosis and perhaps carcinogenesis but as the lung is rela tively radio resistant more lethal damage should be found in other tissues before fibrosis becomes apparent

Simple passage of a dilute soluble radioactive aerosol or gas across the lung membranes has little effect on the lungs unless a high concentration is present in the lungs However krypton and tritium have high specific activity and a single breath of pure tritium gives a surface dose to lung tissue of about 4 000 rep/second and a 3 second inhalation of gaseous T O would result in an integrated total body dose of 3 000 10 000 rep

Inhalation of an insoluble aerosol such as plutonium oxide results in a small amount being dissolved in the blood and then deposited in bone The rest moves up the respiratory tract and into the gut as particles with at least 2 different half lives i e about 6 months and a few weeks Alpha par ticles are emitted by $Pu^{39}$ as it decays They irradiate the underlying tissue and leave a narrow streak of dead or dam aged mucosa behind as they move upward Since large numbers of such particles continuously move up the same course radiation is repetitive and may be carcinogenic

Treatment is most effective for isotopes that are most soluble and do not localize in tissues The absorbed isotope should be chelated as quickly as possible and diverted out excretory routes For 1-4 days 1 Gm EDTA is injected in travenously once or twice a day Diuretics renal acidifying agents and saline cathartics may also be given For $As^{74}$ and $Hg^{03}$ *British antilewisite is preferred instead of EDTA* For plutonium a single dose of 25 mg zirconium citrate/kg

Program of Atomic Energy Commission for Control of Inhalation Hazards of Nuclear Energy Operations is presented by H D Bruner and Charles L Dunham[8] (US Atomic Energy Commission Washington D C) The lung is an effective route for introducing substances into the body considering the average daily alveolar ventilation of 9 kg Whether inspired foreign material reaches systemic blood depends on its particle size solubility and some other minor properties By the time air reaches the larynx particles larger than about 5 μ have been strained out by the vibrissae and by impaction of the moist mucous membranes of the upper respiratory tract In the finer bronchioles the particles are 1 μ or less the finest particles reach the alveoli

If the larger particles are insoluble they are removed mechanically by ciliary action and coughing and most are swallowed If they are still insoluble in digestive fluids their effect is negligible but if they become soluble or chelated they may be absorbed into the circulation If directly soluble in body fluids the substance can be absorbed through the alveolar membrane into the pulmonary capillaries Some materials such as coal excite phagocytic action and end up as deposits in the lymph spaces and lymph nodes

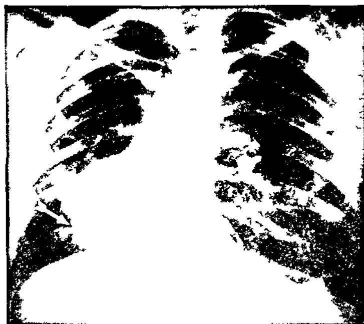
In uranium mines concentrations of radon or radium emanation may reach $6 \times 10^{8}$ curies/L air with averages around $4 \times 10^{9}$ curies/L but the acceptable value of $3 \times 10^{10}$/L can be achieved in most mines A small fraction of inspired radon gas is absorbed into the tissues and before being exhaled is transformed into $Pb^{210}$ It is then deposited in bone and has the typical effect of radium Uranium ore dusts are relatively insoluble but a small part is soluble and tends to localize in the kidney Therefore the limits of concentration in the air are lower than those for other insoluble dusts The mining and processing of thorium raise similar problems but this element may be less hazardous

In air cooled fission reactors the discharged air contains traces of active dusts plus radioactive krypton xenon and argon The activity is diluted to low levels by mixing with large volumes of air in a tall stack but if a fuel element fractures or leaks the fission product mixes into the coolant air going up the stack The most that would happen is the beginning of a discharge of radioactive gases some volatile radio

(8) Dis Chest 33 142 149 February 1958

Of 7 patients with anomalous pulmonary venous drainage of the right lung into the inferior vena cava 6 were asymptomatic and the disorder was discovered after routine chest films Only 1 had a heart murmur In all ECG s were normal Angiocardiography provides the definitive diagnosis

Asymptomatic patients require no treatment In patients with dyspnea recurrent pulmonary infections and plethora



F g 29—C t on l f t l t l oentg n g m how tat f h rt nt right hem th x Not h te t sc t b h g h l h gg g right d ac lh ett ( w) R ght pp l ng fi ld ppea la wh l tt l g sc l t lly p m ent (Court y f St b g I A I t M d 47 2 7 240 A g t 1957 )

of the lungs an associated cardiac lesion probably an atrial septal defect is usually present Cardiac catheterization should be done in symptomatic patients to assess the difficulty

**Massive Atelectasis of Left Lung in Children with Congenital Heart Disease** Most deaths from severe intracardiac congenital disease occur in the 1st year of life Atelectasis of the left lung is a frequent complication before or after sur

body weight is injected intravenously as quickly as possible The radioisotopes of Na H and I are most effectively eliminated by giving large amounts of the stable isotope with diuresis Insoluble isotopes must be removed mechanically If the contamination is under the surface the area is excised Occasionally amputation may be warranted Nasal passages and upper respiratory tract should be rinsed as quickly as possible Clearance of particles from the lung cannot be hurried as yet If most of the activity is localized in 1 lobe of the lung lobectomy probably is indicated

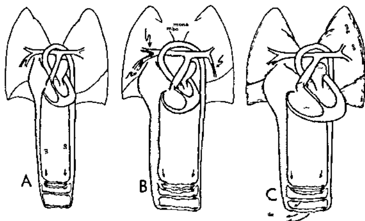
## CONGENITAL ANOMALIES

**Anomalous Pulmonary Venous Drainage of Right Lung into Inferior Vena Cava with Malrotation of Heart Report of Three Cases** is presented by Israel Steinberg[9] (New York Hosp—Cornell Med Center) This is a rare anomaly Before the advent of angiocardiography diagnosis was made only at autopsy or operation The usual finding is prominence of the right atrium extending into the right hemithorax with a multiple branching vessel in the right lung increasing in size from above downward to merge with a broad crescentic channel adjacent to the right cardiac border This finding was a common feature in the 3 patients on conventional frontal chest x rays Angiocardiography shows an anomalous right pulmonary arterial tree and anomalous right pulmonary veins inserting into the inferior vena cava Angiocardiography in the 3 patients revealed such findings and also striking malrotation of the heart into the right hemithorax (Fig 29)

In the development of the superior vena cava system persistence of the left cardinal vein (left superior vena cava) and malformations of the pulmonary veins are closely related Partial anomalous drainage includes insertion of pulmonary veins into the right atrium or its venous tributaries from a lobe or lung It is compatible with long life Complete transposition may produce serious symptoms early in life and long survival is unusual In the total type an atrial septal defect must also exist to sustain life

(9) Ann Int Med 47 2 7 240 August 1957

ington Univ ) This frequent and serious complication of certain chronic illnesses seems to be increasing In general autopsy series it occurs in 5 14% in custodial institutions in 23 1% in cardiac patients in 30% and among patients with congestive failure in 48% It caused or contributed to death in




F g 30—C rt cul t ry ent ft t p lmonary emb l m d n con gest h rt f l e I n m l ul t ry b la (A) tp t f l ft v t ! t d t th m ny m ll rt 1 art l th t gul te g on l d trib t on f fl w Aft rt l p g d l p p llari st d l tone m scula t a d g t t th ac p nt g fl w of enou blood t heart Wh m lt pl or ma p lm y mbol m cc (B) p lmon ry hyp rten d ma k d ght v t ul t n b t f uffi t p g of blood th ough l ng oc d l ft tri l utp t t n d t pp rt l fe cont d t g ty f rt la -cap ll y l y t m n n m l l t m y m ta v n tu t h t t xtent th t nou ong t on es lts O lo d d d t t on f ght e t l m y th b f rth n sed ( cute p lm l ) D pending on d g ee f pulm ry b truct on a d mpet f right vent l pulmon l d g t ft p t f m ny hou Death can oc t y t m When mp t c f l ft a d/ ght ent f d d by myoc d l d ea (C) l t y ffi y d en g t on may be gend d by t lly m l m h n m W th f l f ent l tp t d ca d c d l tat su t d t g ty f p riph l v l m h m g as u es pe tent enou t n t h rt d t l mpound ng of blood v n Co d t n ft h th t fl d filt t on ( d m ) f g g d t d oth gn f c culat ry ffi y be om de t I ea f blood v l m h on h rt f l m y ggr te t t n (C rt y f P k B M d Sm th J R. Am J M d 24 40 -427 M h 19 8 )

25 50% of the patients in these categories Infarction of the lung follows embolism in 50 60% Pulmonary embolism is significantly more frequent in medical than in surgical patients

Pulmonary emboli usually originate as detached portions of venous thrombi from the lower extremities Retardation of venous circulation damage to vessel walls and conditions

gery Laurence M Rivkin Raymond C Read C Walton Lillehei and Richard L Varco[1] (Univ of Minnesota) report 8 cases recognized during 15 months Five patients had ventricular septal defects 1 an aorticopulmonary window 1 a patent ductus arteriosus with coarctation of the aorta and 1 total anomalous pulmonary venous return to the right atrium In 5 atelectasis was present before surgery and in 3 massive collapse of the left lung first appeared during the postoperative period

This form of massive unilateral atelectasis has been noted only in infants with symptomatic congenital heart disease and selectively involves the left lung It has not occurred with the reduced pulmonary blood flow in the tetralogy of Fallot Each of these patients had an increased blood flow through the lungs and serious pulmonary hypertension At surgery the pulmonary artery was observed to be large tense and pulsatile

The mechanism of atelectasis appears to be compression of the left main bronchus by an enlarged left pulmonary artery The size of the left atrium is not significant All the hearts were massively enlarged and encroached on the left lung The prevalence in infancy is probably related to the small lumen and soft nature of the bronchus

Patients with congenital heart disease which produces pulmonary hypertension have varying degrees of left bronchial obstruction seen by chest x ray A high proportion of infants show minor to major atelectasis and/or obstructive emphysema Partial or total collapse of the left lung is an indication for rather than a contraindication to definitive correction of the cardiac anomaly Atelectasis does not resolve spontaneously Surgical mortality is increased in presence of atelectasis but operation is the only hope of saving life

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## PULMONARY EMBOLISM AND INFARCTION

**Pulmonary Embolism and Infarction Review of Physiologic Consequences of Pulmonary Arterial Obstruction** is presented by Brent M Parker and John R Smith (Wash

(1) J Thorac S g 34 116-125 J ly 1957
(2) Am J Med 24 402 4 7 M b 1958

venous return plus diminished cardiac output (Fig 30) When outflow from the right ventricle is suddenly curtailed *by blocked pulmonary arteries or left ventricular failure the* right atrium right ventricle and peripheral veins distend because the heart can no longer accept blood returning through the postarteriolar vasculature Single smaller emboli in normal animals are often relatively innocuous

Pulmonary infarction does not follow ligation of the lung arteries and is unusual after emboli in animals with normal lungs Some alteration of the *intrinsic* circulation must be present Pulmonary congestion infection and diminished *ventilation promote pulmonary infarction* by intrapulmonic circulatory stasis which so impedes irrigation through the connecting bronchial arteries that *collateral blood supply* is restricted or venous drainage becomes inadequate (Fig 31)

Miliary embolization of the lungs invokes severe pulmonary hypertension decline of systemic blood pressure and death with distention of the right cardiac chambers and engorged peripheral veins Widespread constriction of the pulmonary arterioles apparently occurs mediated through sympathetic impulses The effects of most pulmonary emboli on the circulation to the lungs are largely mechanical

*Manifestations of embolic episodes are exceedingly* varied Emboli tend to recur and changing symptoms are evident *The responses are almost entirely referable to mechanical* obstruction of blood flow through the lungs Dyspnea is common It *often begins suddenly and progresses rapidly to* gasping respiration or it may be mild and evanescent Chest pain usually is pleuritic but is often substernal and similar to the pain of myocardial ischemia It is the initial symptom in 12 32% of patients but may be minimal or entirely absent Hypoxia cyanosis circulatory collapse shock tachycardia and paroxysmal cardiac arrhythmias are frequent Acute dilatation of the right ventricle prominent pulsation along the right sternal border loud pulmonic 2d sound pulmonic systolic murmur and diastolic gallop rhythm may all be detected In many instances even the most careful physical and laboratory examination may reveal no indication of pulmonary embolism

*In 75% of the patients with significant emboli* ECG changes may be diagnostic if serial tracings are taken The *typical changes (table) are considered to be the result of*

favoring blood coagulation affect intravascular clotting Any type of heart disease leading to congestion or auricular fibrillation may predispose to thrombus formation either *within the cavity of the right atrium or in peripheral veins* Emboli usually break away from venous thrombi without apparent cause but ambulation after long bedfastness

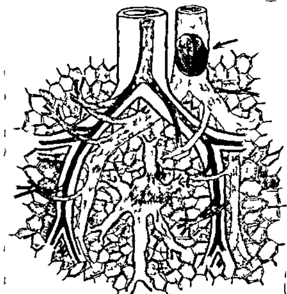


Fig 31—P bl me h m f f mat f f t f l g Th omb t c mbolus (arrow) n p lm n y art y f l g s gment D t d d p lmon y i t r of l b le ll t t s p ong t f t (f m a y ca e) B n h pulmonary ana tomo es no m l l ged d c llate l c ul t n tom ally t ct b t it i p m d th t llat l l t on h be d f at d by mp m t of veno dra g (by onge t ) p m tt g b kdown f t d t l t mbol (Cou te y f P k B M a d Sm th J R Am J Med 24 402 427 M ch 1958)

straining at stool or exertion may aid in detaching venous clots Large clots impact in the larger pulmonary arteries Smaller clots pass to the lower lobar arteries most frequently to the right lower lobe next most frequently to the left lower lobe

Total obstruction of the main pulmonary artery or the two principal branches causes rapid death but as much as 75% occlusion may be tolerated Dilatation of the right cardiac chambers and turgescence of peripheral veins are striking These physiologic responses depend on continued

emboli themselves appear innocuous and not until the multiple obstructions become numerous does right ventricular function deteriorate and circulation become deranged

Treatment of acute embolism and infarction includes morphine or Demerol® to allay anxiety oxygen to reduce anoxia l norepinephrine for shock aminophylline for dyspnea and anticoagulants to prevent further emboli Antibiotics may prevent secondary infections Vena cava ligation is reserved for patients in whom anticoagulant therapy is contraindicated or in whom pulmonary emboli recur despite adequate anticoagulation

► [Attention is called to another excellent recent study of pulmonary embolism and infarction by Israel and Goldstein (Ann Int Med 47 202 1957) Diagnosis of pulmonary embolism despite long established recognition of the frequency and importance of the condition is still more often missed than made The basic difficulty is that it is essentially a clinical diagnosis which lacks any definitive test or pathognomonic sign for its antemortem confirmation Usually when one makes the diagnosis one cannot be sure it is correct even or perhaps particularly if the patient survives from having received the appropriate therapy This is by no means a unique situation in clinical medicine but it is uncommon with respect to common diseases —Ed ]

**Serum Transaminase in Pulmonary Disease and Multiple Infarctions** This test has become popular as a diagnostic measure for acute myocardial infarction However it is less specific than originally believed and increased values have been found in hepatic necrosis obstructive jaundice pancreatitis rheumatic myocarditis and renal infarction John R Walsh Fred L Humoller and Frederick G Gillick[3] (Omaha) observed a rapid increase and an equally rapid decline of serum transaminase (SGO T) activity in other conditions including pulmonary disease

In pulmonary disease most values for SGO T are within normal limits (below 40 units) but in pulmonary infarction values between 40 and 100 may occur especially after the 4th day One patient with fulminating pneumonia had a value of 186 units another with pulmonary infarction had 104 and patients with pulmonary infarction multiple infarctions pneumonia carcinoma of the liver pancreatitis trauma and cirrhosis and 1 patient with uremia frequently had levels between 40 and 100 units

These observations suggest that SGO T levels must be interpreted with care By themselves they are not diagnostic Neither the high level nor the time curve pattern is path

(3) A  I r Med 46 1105 1112 J  1957

acute strain and dilatation of the chambers of the right side of the heart The Q waves in leads II III and aVF with inverted T waves may erroneously suggest posterior myo cardial infarction

Hemoptysis has been reported in 50 65% of patients in two series and as an initial symptom in 5% in another series Cough is noted in about a third of the patients and is prob ably due to irritation of the bronchial mucosa Fever is often

POSSIBLE ECG CHANGES AFTER ACUTE PULMONARY EMBOLISM

S O pattern
Development of S S $S_3$
ST segment depression in leads I and II
Appearance of right axis deviation and change to vertical heart position
Flat or inverted T waves in leads II and III
Peaked P waves in leads II III and aVF
Development of marked clockwise rotation of heart
Appearance of right bundle branch block or right ventricular enlargement patterns
Inverted T waves with ST segment deviations in right precordial leads

present and is unaffected by antibiotics because it is a re sponse to tissue necrosis and inflammation and not to infec tion The physical signs of infarction are similar to those of pneumonia or atelectasis with dulness diminished breath sounds and rales A friction rub may be present

Leukocytosis and elevated erythrocyte sedimentation rates are common The serum bilirubin level is occasionally elevated presumably due to hemolysis of erythrocytes in the hemorrhagic lung infarct Jaundice does not usually appear unless previous hepatic disease was present The typical x ray picture 12 24 hours after embolism shows one or more densities of variable size in the lower lung fields usu ally rounded or linear but occasionally wedge shaped or tri angular They may be compact and highly opaque or hazy and of indistinct outline The angles may be clouded or frank pleural effusion may occur The diaphragm may be elevated on the ipsilateral side

Obstruction of the distal branches of the pulmonary ar teries may occur over a long period with gradually develop ing cor pulmonale Patent portions of the arteries proximal to the emboli have intimal atherosclerotic plaques These patients may show unremitting congestive heart failure frequent cyanosis dyspnea cough and hemoptysis The etiologic diagnosis is usually unsuspected during life The

floss) and many patients are relieved of asthma when pillows and furniture stuffed with kapok are removed from the home Importation of kapok from Java to the United States is curtailed and this type of asthma is now less common Development and maintenance of clinical sensitivity requires exposure

Drugs of all kinds are recognized as specific sensitizers Horse or rabbit serum as such is no longer used in medicine but the classic mechanism which applies to serum disease develops when penicillin is given too freely and too long The reaction appears in 7 10 days When the diminishing amount of circulating antigen (penicillin) comes into relation with the increasing amount of penicillin antibody a toxic product is formed causing fever urticaria and/or joint pains When the patient is sensitive antibodies come quicker and the reaction sooner If the patient is extremely sensitive the reaction may develop at once as anaphylactic shock The best treatment of drug reaction is prevention Before giving a new drug the doctor must ascertain whether the patient is subject to allergies and is likely to acquire sensitivities and whether the patient has ever taken that drug before and if so if it caused any reaction If the history is reliable it will tell more than any objective test

All is not allergy that wheezes Acute respiratory infections may be the primary cause of an attack which begins and ends with the infection Bacterial allergy is hard to prove In young patients the new infection lowers the threshold to make a slight sensitivity to a substance become clinically effective This is the asthmatic bronchitis a series of wheezy colds which is so common Secondary infections due to bacteria or viruses may complicate the simple picture of allergy to prolong the attack The pale polypoid membranes of the paranasal sinuses are part of the process not the cause of it Removing nasal polyps will relieve the stuffy nose and the asthma at least for a time Operations on the sinuses will bring relief but when asthma recurs after a sinus operation it is usually worse than before

Emotional disturbances can excite asthma in patients with an asthma background They often develop on top of the allergy or infection Allergy infections and emotions can each produce asthma provided the patient has the proper back

ognomonic of myocardial infarction and they can be mimicked in other unrelated diseases The test is valuable corroboratively when evaluated with the clinical picture and correlated with the ECG A normal SGO T level does not exclude the diagnosis of myocardial infarction but usually indicates that the specimen was taken too early or too late Increased SGO T levels can be found in pulmonary disease but usually occur later than in myocardial infarction Levels above 100 units are more suggestive of myocardial infarction but pulmonary disease may occasionally cause similar levels

## BRONCHIAL ASTHMA

**Experiences with Asthma Problem** are reviewed by Francis M Rackemann[4] (Boston) Until recent years the study of clinical allergy was limited to the study of skin tests The scratch method and intradermal injections are useful and should be available If the history indicates that the sensitivity may be to dust or food substances outside the body the scratch method must be used first and the more delicate intradermal method applied only if the scratch is negative If it appears that the cause is intrinsic and that sensitivity to dust or food cannot explain the symptoms the intradermal method can be used directly In such cases the tests are usually negative and allergy can be excluded Skin tests are not as reliable as first thought False positives with no relation to the history are common In other cases skin tests may be negative though clinical evidence of sensitivity is well defined Skin tests are tests of the skin they may or may not reflect sensitivity in other tissues

Patients sensitive to house dust can often benefit by changing to a different room and bed preferably with a sponge rubber mattress and pillow and achieve long lasting results The whole subject of mold allergy is difficult because of the enormous number and variety of molds but the problems are closely related to those of house dust Molds can break down vegetable fibers particularly those of kapok (called silk

(4) M Clin North Amer a 41 1039 1048 July 1957

► [The asthma problem seen in the perspective of nearly half a century since Rackemann began his work in allergy in 1912 This is however not merely a historical summary Rather it is a succinct analysis of the present status of a perplexing problem —Ed ]

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## BRONCHIECTASIS

**Prolonged Antibiotic Treatment of Severe Bronchiectasis** is considered in a report by a subcommittee of the Antibiotics Clinical Trials (Nontuberculous) Committee of the Medical Research Council[5] Antibiotics are effective in many acute respiratory infections but chronic bronchial infections particularly bronchiectasis are more difficult to treat Individual patients may respond to initial treatment but its cessation is usually followed by early relapse and re establishment of infection

In a controlled trial 122 patients with bronchiectasis received 1 of 3 treatments at random 38 received penicillin 44 oxytetracycline and 40 lactose The drugs were in indistinguishable 0 25 Gm capsules given as 2 capsules 4 times daily for 2 days of each week for 1 year Volume of 24 hour sputum and severity of cough dyspnea hemoptysis and disability were measured regularly The groups were similar in age distribution history of previous respiratory illness and extent of involvement as determined by a recent bronchogram

During the year each group showed a reduction in sputum volume greater for the pus than for the mucus fraction and most marked in the group receiving oxytetracycline Each group showed some reduction in severity of cough and dyspnea and in number of hemoptyses Disability measured by number of days off work episodes of fever and number of days confined to bed was less in all groups during the year of treatment but the degree of improvement was greatest in the group receiving oxytetracycline No serious toxic effects were noted in any group

In general oxytetracycline was beneficial and more effective than oral penicillin in severe chronic bronchiectasis but it is expensive The response obtained and expense entailed do not justify widespread use of long term oxytetra

(5) B M J 2 255 259 Aug 3 1957

ground Thus far treatment for asthma has been directed toward these exciting causes If asthma is to be cured the background must be modified

Chronic vasomotor rhinitis eczema and urticaria have the same variety of causes requiring the same careful study of the history and the same general principles of treatment as asthma These different symptom complexes are closely related and may occur in the same patient A common story is eczema in infancy hay fever in the late teens and asthma in the 40 s Can not asthma or rhinitis eczema or urticaria be considered patterns which develop on a certain background?

Intrinsic asthma implies that the cause is something which the patient carries within himself at all times and in all places Typically it begins suddenly after age 40 and there is no indication of allergy to dusts foods or drugs Skin tests are negative except occasional slight irritative reactions to house dust An eosinophilia of 10 20% may be present Nose and sputum cultures show normal flora No one organism is found with any regularity Attempts with injections of autogenous vaccines provoked an attack of asthma in 7 of 45 trials Emotional factors in these patients are concerned with the result of the process rather than the cause

Neither allergy infection psychogenic factors nor combinations of these can explain the clinical picture and some unknown fourth factor must be operative Follow up studies show that about one third of patients are free from asthma and another third greatly improved following such different treatments as potassium iodide autogenous and stock vaccines and removal of focal infections Correction of obesity or constipation reduction of business pressure better relations with the family improved daily hygiene regulation of meals rest and exercise outdoors have been effective

Asthma rhinitis eczema and urticaria will be better understood when the disorders of immunology physiology and chemistry in these symptoms are known Whatever the process it apparently is reversible The problem ought not to be as difficult as now appears Advances in other fields of medical science some day will be applied to the study of the wheeze the sneeze and the itch Until then imagination and new ideas wild and tame are needed for better understanding of the problems of allergy

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**Bronchospasm in Bronchography** may be misinterpreted as bronchiectasis and lead to unwarranted excisional surgery according to Thomas H Hewlett Anthony J Puglisi and Warner F Bowers[6] (Brooke Army Hosp Ft Sam Houston Tex ) A single bronchogram reveals the anatomic state of the bronchi when the film was exposed but cannot differentiate between reversible and irreversible changes Interpretation of bronchograms and the decision for surgery is often delegated to the younger men in a training program and a single bronchogram may be misinterpreted

The factors which may interfere with bronchial filling are acute respiratory infections emphysema and atelectasis Chronic bronchitis or asthma may cause beading in the bronchi and irregularities of caliber Bronchospasm during bronchography is not uncommon In 79 bronchographic studies it occurred in 7 patients Presentation of the films to experienced clinicians resulted in disagreement on the initial diagnosis of bronchiectasis When repeated the bronchograms were normal

Bronchospasm is usually associated with asthma most frequently diagnosed by a history of attacks of respiratory distress wheezing and rales Bronchograms may show bronchospasm misinterpreted as bronchiectasis because of cylindric dilatation (Fig 32) Repeat studies (Fig 33) are normal if bronchospasm caused the initial abnormality

The typical findings in bronchospasm are bronchial dilatation (hydrostatic) in the primary bronchi and portions of the secondary bronchi spasm of the tertiary and distal bronchi obstructing the flow of the contrast medium with nonfilling of the spastic bronchi normal space relations between the 1st and 2d division bronchi indicating the existence of aerated lung parenchyma bronchiolar and alveolar filling only patchy when evident distal to the zone of dilatation and proximal narrowing of a major bronchus never visualized In contrast bronchiectasis is characterized

(6) J Thora S g 33 609 616 M y 1957

by marked cylindric dilatation with complete loss of the normal tapering tendency saccular areas in direct continuity with the dilated bronchus crowding of bronchi because the pulmonary parenchyma in the involved area occupies a

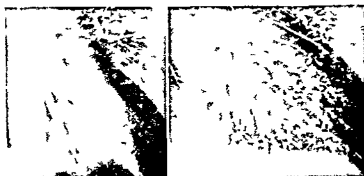


Fig 3 (left) —Initial right anterior oblique bronchogram revealing spasm of lingula and left lower lobe

Fig 31 (right) —Repeat right anterior oblique bronchogram normal pattern (Courtesy of Hewlett, T H. et al J Thorac Surg 33 609-616 May 19 7)

decreased space decreased or absent bronchiolar and alveolar filling and proximal bronchial narrowing evident or nonevident Horizontal obstruction to flow is not seen

► [The misinterpretation of bronchograms is common. This report focuses attention on one of the most important causes of error —Ed ]

**Significance of Bronchiectasis Associated with Pulmonary Tuberculosis** John K Curtis[7] (VA Hosp Madison Wis ) studied the clinical course x rays bacteriology and pathology of resected specimens in 1 000 cases of pulmonary tuberculosis Three principal factors favor the dilation distortion and disorganization of bronchial walls and tuberculous involvement of bronchi The least frequent form is usually established in childhood and is due to enlarged tuberculous hilar nodes compressing a bronchus inflammation surrounding these areas or perforation of the bronchus Partial obstruction with cough pooling of secretions and tubercle formation in the more distal portion of the bronchial tree lead to bronchiectasis The commonest cause is severe infiltration of the lung with tuberculous disease often associated with a cavitary component Residual bronchiectasis is frequent though the parenchymal disease is cured The third type is

(7) Am J Med 22 894 903 June, 1957

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(6) J Tho a c S rg 33 609 616 May 1957

Among 13 patients (table) in whom the sputum remained positive or who relapsed after segmental resection planigrams revealed bronchiectasis in 6 bronchograms revealed bronchiectasis in 8 and 9 had further resections All but 1 had had preoperative chemotherapy for 6 months or more

Segmental resection is an accepted surgical procedure in treatment of pulmonary tuberculosis Careful preoperative appraisal of the involved lobe by planigrams and bronchograms is indicated to avoid complications associated with the type of tuberculous bronchiectasis which approaches dangerously near the intersegmental plane of dissection

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## NEOPLASMS

**Aortic Body Tumor (Chemodectoma) of Mediastinum Report of Case and Review of Literature** are presented by Harvey Mendelow and Morris Slobodkin[8] (Maimonides Hosp Brooklyn) Several hundred cases of carotid body tumor have been reported and several of the glomus jugulare and the ganglion nodosum but not until 1950 was the first aortic body tumor described in man This is the 7th case recorded

The carotid bodies are small ovoid nodules on the medial aspect of the bifurcation of the common carotid arteries There are at least 4 aortic bodies 1 near the pulmonary end of the obliterated ductus arteriosus 1 near the origin of the left coronary artery 1 at the bifurcation of the innominate artery or lateral to the origin of the right subclavian artery *and 1 at the anterolateral surface of the left* side of the aortic arch near the root of the left subclavian artery The glomus jugulare or paraganglion tympanicum is in the adventitia of the jugular bulb at the bony floor of the middle ear associated with the tympanic ramus of the 9th cranial nerve Similar cell clusters are associated with the ganglion nodosum of the vagus nerve at the level of the 1st and 2d cervical vertebrae near the base of the skull All these are part of a group or system which differs from the chromaffin tissues

The carotid and aortic bodies function as chemoreceptors sensitive to changes in the chemical composition of the circulating blood especially *pH oxygen and carbon dioxide*

(8) Cancer 10 1003-1014 Sept-Oct. 1957

tuberculous endobronchitis leading to destructive changes in the bronchial walls and thus to bronchiectasis

Tuberculous lesions are closely associated with a subsequent finding of bronchiectasis in the same areas Incidence is high in the upper lobes and in this area symptoms may be minimal Clinical features when present are persistent cough

Data on 13 Patients* with Bacteriologic Relapses or Positive Secretions after Segmental Resection

| | | |
|---|---|---|
| Diagnosis | | |
| Moderately advanced | 6 | |
| Far advanced | 7 | |
| Average age of patient | 34 5 | years |
| Average duration of disease | 18 | months |
| Average duration of chemotherapy before surgery | 13 | months |
| Continuous combined therapy before surgery | 11 | patients |
| Relapse after discharge | 6 | patients |
| Positive secretions in hospital after surgery | 7 | patients |
| Resistant organisms in sputum or resected specimen (12 tested) | 6 | patients |

*Eight patients from [illegible] of over 500 segmental resections 5 from other hospitals Detailed follow up not yet available on the 500

and purulent sputum Hemoptysis may be troublesome Protracted bronchitis following upper respiratory infection is common and sputum is most apt to show tubercle bacilli at that time

The pathologic features are unique Tubercles often lie close to the epithelial surface and only slight ulceration may liberate caseous material into the bronchial tree Many bronchiectatic lesions communicate with cavities or liquefying nodular disease a source of long continued positive secretions The bronchial walls may be thickened and scarring tends to distort and pull diseased bronchi together Tubercle bacilli in these areas may be protected from adequate concentrations of chemotherapeutic agents and survive long periods of even intensive antimicrobial therapy

Bronchiectasis is a common cause of relapse or surgical failure in patients who have had resection of the tuberculous portions of the lungs The saccular bulbous type is particularly hazardous if a caseous focus extends across the segmental plane The thick irregular infected walls may remain open unless carefully sutured or may break open again

**Sensory and Motor Neuropathy in Lung Cancer** is reported by E Uehlinger[9] (Univ of Zurich) Sensory neuropathy and polyneuritis have been observed in combination with only intrathoracic cancer (lung and esophageal cancer) About 2% of lung cancers are complicated by spinocerebellar ataxia sensory neuropathy polyneuritis and neuromuscular disturbances The relation is unknown these changes are not due to carcinomatous invasion of the nervous system

Woman 58 became ill with severe polyneuritis She progressively lost sensibility vibration and position sense with paresthesias and



F g 36—T sect on th ough l mb co d h w ompl t degen rat n f posterio l mn (G ll and P dach col mn) d part l d gen rat on f pinoc bella t act d ed f om ×7 5 (C rtesy f Uehling E S hwei med. W hnsch 87 1580 1585 Dec mbe 19 7)

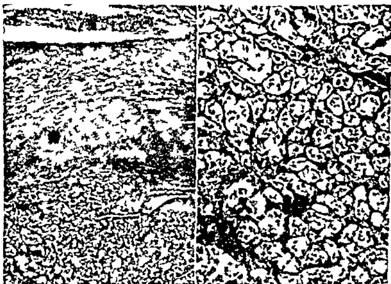
muscle atrophy Autopsy showed a chestnut sized undifferentiated small cell bronchial carcinoma in the left lower lobe near the hilus with a solitary metastasis to a hilar lymph node The severe sensory loss was due to an affection of the spinal ganglions with a progressive devitalization of the ganglion cells and their axon cylinders There was also degeneration of the dorsal spinal roots the funiculus of Goll and Burdach and the tractus spinocerebellaris dorsalis with Waller s degeneration of the peripheral nerves (Fig 36) The central and peripheral nervous systems were free from cancer

Since the destruction of the spinal ganglions cannot be due to a cancerous invasion of the nervous system it is suggested that the changes be called metacarcinomatous neuromyopathy or funicular sclerosis In general the metacarcinomatous changes may present themselves as sensory motor or polyneuritic neuropathies though there are also mixed

(9) S t z med. W h sch 87 1580 1585 Decembe 19 7

concentration and aid regulation of blood flow and respiration

Clinically aortic body tumors are remarkably silent Three were discovered on routine chest film as incidental findings at autopsy Only 2 of the 7 patients had symptoms of pain No physiologic or endocrine effects were produced Aortic body tumors appear as a globular or ovoid, moderate sized



F g 34 (left) —Low power ew sh w g clo e adh r n of t mo to dv t tı f th s l g rtery b n b r d ed f om ×35

F g 35 ( ght) —C n l p ttern f tumo mpo ed f w ll d ma cat d n t f p thel o d c lls et a la st ma p d c ng lenomat p ttern r du ed from ×100

(C u t of Mend low H d Sl bodk n M C n e 10 1008 1014 S pt O t 1957 )

well defined and encapsulated mass but the capsule often is densely adherent to the wall of a large blood vessel Surrounding structures may be invaded Microscopic appearance is characteristic (Figs 34 and 35) Metastases have been demonstrated in carotid body vagal body and glomus jugulare chemodectomas These tumors are resistant to radiotherapy Surgery is dangerous because of the extreme vascularity of the tumor Even if removal is impossible the apparent slow course and clinically silent behavior suggest that their presence is not incompatible with long life

communication between the neoplasm and bronchial lumens stenosis of the bronchi and misinterpretation of smears Secondary factors were location of the carcinoma histologic type quality and quantity of specimens presence of secondary inflammation and type of specimen (sputum or bronchial aspirate) Sputum was superior to bronchial aspirates especially in diagnosis of cancers in the upper lobes of the lungs or those located peripherally

**Combined Roentgen Therapy and Nitrogen Mustard in Carcinoma of Lung as Compared to Other Methods** Cure for carcinoma of the lung is surgical in all but a few instances Roentgen therapy is generally palliative and the optimal dosage has not yet been determined Development of supervoltage megavoltage betatron linear accelerator and isotope teletherapy has tended toward higher tumor doses but a correlative clinical effect has not been generally recognized

K L Krabbenhoft and T Leucutia (Harper Hosp Detroit) analyzed various methods of treatment exclusive of surgery in 393 histologically proved cases treated between 1922 and 1956 Originally only 200 kv therapy was used followed by 550 kv in 1932 Between 1929 and 1945 30 patients were treated with roentgen therapy plus intrabronchial radium Since 1947 226 patients received roentgen therapy and nitrogen mustard The latter is administered 0 1 mg/kg body weight daily for 4 consecutive days into the tubing of an intravenous saline infusion

The concomitant therapy of nitrogen mustard and irradiation (both 200 kv and 550 kv) improved the early survival rates increasing the per cent of patients living up to 1 year from 50 to 58 4 in undifferentiated and oat cell types This definite but small increase warrants continuation of a program of combined roentgen therapy and nitrogen mustard in managing inoperable carcinoma of the lung Lesions of oat cell or undifferentiated cell type respond better to all forms of therapy exclusive of surgery but particularly well to combined roentgen and nitrogen mustard therapy

**Treatment of Cancer of Lung by Interstitial Implantation** Among 2 075 patients reported on by various surgeons 43% showed non resectable lung cancer at operation With this

( ) Am J Roe tg 1 9 431 504 M h 1958

forms The cerebrospinal fluid may show at least temporarily increase in proteins with or without increased cell count The gold sol curve reveals severe parenchymatous changes

► [The association of sensory neuropathy and myopathy with lung cancer was first fully described 10 years ago by Denny Brown Since then the syndrome has become established though it is not well known Uehlinger estimates the frequency of this complication to be 1 2% in cases of lung cancer The posterior column degeneration in this instance he points out is more extensive than is usual in tabes dorsalis —Ed ]

**False Negative Reports in Cytologic Diagnosis of Cancer of Lung** To assess the factors responsible for these false negative reports William O Umiker[1] (Univ of Michigan) examined the sputums or bronchial secretions of 217 patients with miscellaneous pulmonary diseases by the Papanicolaou technic Of these patients 42 had cancer of the lung confirmed histologically Smears from 37 of these 42 were positive or suspected of having malignant cells The 5 false negative instances were thus 12% of the cases of cancer of the lung

The best cytologic results are obtained with neoplasms of main stem bronchi but most such tumors are readily detected by bronchoscopy Cytodiagnosis is 23% more accurate in cancer of the lower lobe than in cancer of the upper lobe When only bronchial aspirates or washings are used the difference is even more significant Peripheral neoplasms are less likely to yield positive smears than are those in the hilar region This may be explained by the smaller bronchi involved and the lack of demonstrable communication with a bronchus in some cases Though the poorest results were obtained with neoplasms in an upper lobe or peripheral position or both the smear technic is of the greatest value in detecting these cancers since bronchoscopy is seldom successful in these areas

Malignant squamous cells are readily recognized in smears because of their large size pleomorphism and characteristic keratin Small undifferentiated carcinoma cells are easily overlooked in smears even if many are present They are easily confused with mononucleated leukocytes Results improve as cytologists gain familiarity with the microscopic characteristics of these cells

The primary causes of false positive results were absent

(1) Am J Cl P th 8 37 45 J ly 1957

## PULMONARY MYCOSES

**Fungous Infections of Lung with Septic Course** were ob served in 8 patients in less than a year by E Wollheim and H Braun[4] (Univ of Wurzburg) Diagnosis was con firmed in all by repeated sputum examinations Fungous disease was secondary to pulmonary carcinoma and to severe *tuberculosis in 2 patients The other 6 had primary pneumo* mycosis In 7 moniliasis was due to Candida albicans or C tropicalis In 1 C albicans and aspergillus were found In 2 blood cultures yielded C ablicans and aspergillus In 3 pa tients material obtained at autopsy from viscera pulmonary lymph nodes aortic valves and kidneys yielded cultures of the same organisms isolated from sputum during life

Primary moniliasis of the lungs occurred only in patients who had had antibiotic treatment especially with penicillin This treatment had led to such extensive elimination of the normal bacterial flora that proliferation of various types of monilia from the buccal cavity was not inhibited In 2 pa tients mucosal lesions of the upper air passages could be attributed to fungous colonies Specific tissue changes in other organs were not observed even in patients in whom the organism was isolated by culture from autopsy material

According to the x rays pulmonary moniliasis begins as bronchitis and peribronchitis with hilar lymph node swell ing and increasing signs of bronchial and peribronchial in filtration The next stage is the bronchopulmonary with coughing and tenacious clear discharge sometimes tinged with blood New lesions appear at different sites along with partially healed infiltrations In advanced cases dyspnea and symptoms of acute cor pulmonale become prominent

Although benign cases have been reported in general the course appears to be progressive with a high mortality Res olution of pneumonic lesions was observed only in the pa tient with aspergillus infection

Treatment at present is not satisfactory although develop ment of specific antibiotics (e g trichomycin) seems prom

(4) D tsch m d W h sch 82 1397 1399 A g 30 1957

type of lesion average survival is under 5 5 months Thoracotomy allows interstitial implantation of radioactive sources that deliver a high tumor dose with less damage to normal tissues than do other radiotherapeutic methods Radioactive gold and iridium have many advantages over radon seeds Eugene E Cliffton Ulrich K Henschke and Henry H Selby[3] (Mem l Center for Cancer New York) report on 140 patients with histologically proved cancer who had radon seeds implanted interstitially at thoracotomy between 1941 and 1955 Three implants were done before 1947 9 in 1949 15 in 1950 31 in 1951 20 in 1952 22 in 1953 20 in 1954 and 20 in 1955

Eleven had tumors other than primary bronchogenic Six of the 11 had metastatic lung lesions (3 from the breast and 1 each from the kidney thyroid and colon) 2 had carcinoma of the esophagus 1 had a reticulum cell sarcoma 1 had a Hodgkin s tumor and 1 had a teratoma in the anterior mediastinum Four of the 11 were still living 23 25 44 and 48 *months after implantation* Average *survival was over 18* months in the others Interstitial implantation should be considered if thoracotomy is done for metastases

Of the 129 with bronchogenic carcinoma 21 (16%) had resection and implantation Among 9 with pneumonectomy and implantation operative mortality was 44% average survival 4 7 and median survival 6 5 months Among 12 with limited resection or lobectomy with implantation postoperative mortality was 25% average survival 17 4 and median survival 7 months Among 108 with implant without resection operative mortality was 5 6% average survival 10 3 and median survival 7 months Slight differences in survival were found among patients with histologically different tumors treated by implantation alone

Among 5 with superior sulcus tumors treated by implantation without resection no deaths occurred average survival was 27 8 and median survival 29 months Palliation was good in all One patient was living well and free from pain 4 2/3 years after implantation

Average and median survival rate for patients with bronchogenic carcinoma treated by implants without resection showed no definite trend over the years

(3) Cancer 11 9 17 Jan F b 1958

such as size of the hyphae type of branching and absence of septation sporangia and spores

Man 35 had a diagnosis of acute histiocytic leukemia with acute lower lobe pneumonia in 1954 He was treated intensively with antibiotics and transfusions Cortisone was begun in April 1955 but fever continued fatigue increased and bleeding became severe He was admitted again in June 1955 X ray of the chest was normal He had anemia and thrombocytopenia the white blood cell count was 7 400 with 30% blast cells He was treated with Dilantin® penicillin ACTH prednisone blood transfusions and concentrated thromboplastic factor A repeat x ray shortly before death revealed ill defined somewhat irregular small areas of increased density extending into the peripheral lung field without definite evidence of consolidation He died 28 days after admission

At autopsy the pericardium and pleura showed many adhesions The lungs contained many brownish red nodules in both apexes Many cavities of various size were lined by a gray thick granular material Microscopic examination showed multiple areas of thick clumps of branching nonseptate mycelia infiltrating into the surrounding lung tissue from alveoli and thrombosed vessels (Fig 37)

The final anatomic diagnoses were histiocytic leukemia bronchopneumonia secondary to overwhelming mixed bacterial and mycotic (mucormycosis) infection and massive gastrointestinal hemorrhage

**Surgical Treatment of Chronic Progressive Pulmonary Histoplasmosis** This disease may be acute chronic latent or recurrent and may involve any and all organs of the body John W Polk J A Cubiles (Missouri State Sanatorium Mt Vernon) and W W Buckingham[6] (Missouri State Sanatorium Kansas City) report on 21 patients with proved pulmonary histoplasmosis each treated by some type of surgery who demonstrate the wide variety of pathologic pulmonary manifestations which are possible and the necessity of excluding bronchogenic carcinoma pulmonary tuberculosis bronchiectasis and empyema in differential diagnosis

Twelve patients had cavities varying from 2 cm to complete destruction of the left upper lobe Some showed small outcropping cavities from the central or larger one Intense inflammation was present in the pleura and extrapleural resection was required in 12 patients Two had definite bronchiectasis and 1 had bronchiectasis middle lobe syndrome and atelectasis Two showed marked cystic changes Two had empyema and both had large bronchopleural fistulas In only 1 was Histoplasma capsulatum cultured from empyema fluid

(6) J Tho S g 34 3 3 343 S pt mb 1957

ising All the usual antibiotics should be withdrawn In mild cases iodine treatment should be used to aid in bringing up secretions In severe cases a trial with stilbamidine or pentamidine is worth while although in some cases these may cause severe local reactions

**Pulmonary Mucormycosis in Acute Histiocytic Leukemia** A case is reported by Mario Stefanini and Salvatore Allegra[5] (Boston) Many species of the Mucoraceae are common laboratory contaminants but the genus Rhizopus may be pathogenic for man Only 21 previous cases of pulmonary mucormycosis have been reported 6 in patients who had leukemia The introduction of antibiotics chemotherapy and



Fig 37.—Typical pulmonary lesions showing *mycotic thrombus* adherent to wall of pulmonary arterial vessel Phloxine and methylene blue reduced from ×150 (Courtesy of Stefanini M and Allegra S)

adrenocortical steroids has greatly altered the natural course of acute leukemia Temporary remissions are frequent but so are new complications

In this case as in most which have been reported diagnosis was established only at autopsy The fungus was not identified by culture The classic findings at histologic examination are penetration into arterial walls producing thrombosis and infarction mycotic spread within the bronchi and alveoli producing mycotic bronchitis and pneumonia and certain morphologic characteristics of the fungus

(5) New England J Med 256 10 6 1030 May 30 1957

toward normal and the increase was well correlated with clinical improvement

There are three apparent means whereby the residual volume can be reduced (1) encroachment from outside the lung as in pneumoperitoneum (2) filling of alveolar spaces as in acute pulmonary edema pulmonary vascular congestion consolidation fibrosis of the alveolus alveolar septum or interstitial tissue and (3) bronchial or bronchiolar obstruction with collapse of distal segments

Much of the physiologic impairment in sarcoid could be due to a low grade inflammatory response with its proliferative and exudative components rather than to fibrosis The end result of pulmonary sarcoidosis is extensive fibrosis which results in greatly impaired function The effect of racemic epinephrine aerosols and steroids and the observed hyperventilation are explained by the inflammatory character of the sarcoid granuloma rather than by fibrosis Resolution of the inflammation is enhanced by steroids

Woman 27 had progressive dyspnea and productive cough Liver biopsy revealed many granulomas without necrosis Residual volume was 0 570 L maximal breathing capacity 35 L/min and the 7 minute end tidal nitrogen level was 5 6% indicating poor intrapulmonary distribution of respiratory gases Racemic epinephrine aerosol dramatically increased the residual volume and maximal breathing capacity When the effects of the aerosol were dissipated the pulmonary function reverted to its former level First ACTH then cortisone improved the function tests to the same degree as did the aerosol but the improvement was maintained Repeat liver biopsy after 6 weeks of ACTH and cortisone showed only normal liver tissue

► [There is much uncertainty expressed in the recent literature on sarcoidosis regarding whether or not treatment with steroid hormones is beneficial Gray and Gray are cautious in their conclusions but on the basis of these well studied cases they believe that hormone therapy was of value despite a fatal termination in 2 of their treated cases —Ed ]

**Pulmonary Function in Sarcoidosis before and after ACTH and Cortisone Therapy** was studied by Inga Rudberg Roos and Bjorn Erik Roos[8] (Östersund Sweden) in 13 men and 8 women aged 28-65 Only 8 had symptoms for under 18 months and 11 had had previous ACTH or cortisone therapy Biopsies were positive in 17 and clinical course or x rays were diagnostic in the others Most patients were treated for 1 month with long acting ACTH and either cortisone hydrocortisone or prednisone None of the patients showed complications necessitating discontinuance of

(8) Acta t be scand 35 49 66 1958

Pulmonary resection is the most definite if not the only method for successful therapy in pulmonary histoplasmosis Medical therapy has been disappointing The most positive indication for surgery is a localized lesion Focal coin le sions are no problem regardless of the type of resection used Cavitary histoplasmosis probably warrants lobectomy though several segmental resections have been successful A person weakened by histoplasmosis and remaining in a hospital for the tuberculous with or without tuberculosis diagnosed should receive adequate antituberculous therapy before and after resection If x rays show a process resem bling tuberculosis and the skin test is positive for histo plasmin and negative for tuberculin the diagnosis is con sidered to be pulmonary histoplasmosis until proved other wise The two diseases may coexist

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## SARCOIDOSIS

**Pulmonary Sarcoidosis Physiopathologic Analysis** is presented by Frank D Gray Jr and Frieda G Gray[7] (Yale Univ ) Pulmonary function studies in patients with sar coidosis show an alveolar capillary block Hyperventilation is prominent but intrapulmonary gas distribution is not im paired to the same degree as in emphysema Residual lung volume is significant because it reflects the architecture of the lung better than any other test in current use In pul monary sarcoidosis residual lung volumes have been report ed as high, normal or low In a careful study of 23 docu mented cases 19 patients were found to have remarkably low residual lung volumes

Among 11 patients studied before and after they inhaled bronchodilating aerosol residual volume increased in 7 Maximal breathing capacity also increased This is in con trast with other chronic lung diseases in which broncho dilators have no effect or decrease the residual volume

In 9 of the 23 patients symptoms were severe enough to warrant treatment with ACTH or cortisone for 1 6 years and 7 improved Steroid therapy as well as racemic epineph rine aerosol increased the abnormally low residual volumes

(7) J Chron Dis 6 572 580 December 1957

of erythema nodosum arthritis uveitis or parotitis Apart from erythema nodosum 30 patients had clinical signs of extrapulmonary sarcoidosis (Table 2) in 22 of the 30 these signs were present on first examination Most important were the ocular lesions Sensitivity to tuberculin was usually absent or low Of 62 patients tested 23 gave a negative reaction to 100 tuberculin units Insensitivity to tuberculin

TABLE 2—HILAR NODE SARCOIDOSIS EXTRAPULMONARY SARCOIDOSIS IN 30 PATIENTS

| | |
|---|---|
| Ocular sarcoidosis | 17 |
| Skin sarcoids | 7 |
| Enlarged superficial lymph nodes | 5 |
| Peripheral nerve involvement | 5 |
| Enlarged salivary glands | 3 |
| Splenomegaly | 2 |
| Hepatomegaly | 1 |
| Bone sarcoidosis (x ray) | 1 |

was not correlated with degree or duration of node enlargement

The bronchopulmonary nodes at the divisions of both main bronchi were always enlarged and the superior tracheobronchial and paratracheal nodes were enlarged in 39 of the 66 patients Bronchi were rarely distorted and no evidence of bronchial obstruction was found clinically or by x ray

TABLE 3—HILAR NODE SARCOIDOSIS RADIOLOGIC COURSE IN 66 PATIENTS

| Course | No Patients |
|---|---|
| Lung fields remained normal | 45 |
| Nodal shadows cleared | 33 |
| Unchanged (follow up < 2 yr ) | 9 |
| (follow up 1 9 yr ) | 3 |
| Pulmonary shadows developed | 21 |
| Normal radiograph eventually | 12 |
| Improved radiograph eventually | 1 |
| Unchanged (follow up < 38/12) | 2 |
| Increasing shadows | 3 |
| Pulmonary fibrosis (advanced) | 3 |

By x ray (Table 3) the hilar nodes in most patients reached maximal size by the time they were detected Only 7 enlarged further Often they remained the same and then rapidly diminished over the next 3 months Lung fields re

the drug and body weight did not increase appreciably All reported subjective improvement with amelioration of dyspnea decrease in cough and less chest oppression

Pulmonary function was measured spirometrically Of the 8 with symptoms far under 18 months 5 improved in pulmonary function and 3 deteriorated None of the 13 with symptoms for longer periods improved after treatment Though there was no proof that cortisone or ACTH appreciably changed the course of pulmonary sarcoidosis the good results in 5 of 8 with fairly recent symptoms justifies further trials in selected cases

**Hilar Lymph Nodes in Sarcoidosis With Special Reference to Prognosis** Hugh Smellie and Clifford Hoyle[9] (King s College Hosp London) followed 200 patients with sarcoidosis 66 of whom had x ray evidence of enlarged hilar lymph nodes when first seen though the lung fields were normal Diagnosis was confirmed histologically in 34 of the 66 patients in liver biopsy specimens conjunctiva skin superficial lymph nodes and/or bronchi Diagnosis also depended on the x ray appearance absence of Mycobacterium tuberculosis on culture usually a low or absent sensitivity to tuberculin normal white blood cell counts and no debilitation

TABLE 1—HILAR NODE SARCOIDOSIS PRESENTATION IN 66 PATIENTS

| | | |
|---|---|---|
| Symptoms referable to sarcoidosis | | 28 |
| Erythema nodosum | 13 | |
| Uveitis | 9 | |
| Skin sarcoids | 3 | |
| Polyarthritis | 2 | |
| Parotitis | 1 | |
| Route radiography | | 26 |
| Various symptoms | | 12 |
| Chest pain | 5 | |
| Lassitude | 2 | |
| Wheezing (in asthmatics) | 2 | |
| Cough | 2 | |
| Dyspnea | 1 | |
| Total | | 66 |

The presenting symptoms (Table 1) in 28 patients were those usually associated with sarcoidosis No abnormal signs *were found* in the chest Pyrexia and increased sedimentation rates were present only during the brief invasive stage

(9) Lancet 2 66-70 July 13 1957

# TUBERCULOSIS

**Why Have We Not Accepted BCG Vaccination? A Report by the Medical Advisory Committee of Research Foundation**[1] estimate that some 150 000 000 persons have been vaccinated with BCG throughout the world including a rigorously controlled series in Great Britain The results were unequivocal in the marked reduction of the incidence of tuberculosis in the vaccinated persons as compared with the nonvaccinated tuberculin negative controls

With increase in the standard of living and the advent of chemotherapy and improved surgery the mortality from tuberculosis in the United States has dropped dramatically but the number of newly reported cases remains high Tuberculosis is still a serious problem in many areas and an effective vaccine would be a material aid

The multiple puncture method has practically eliminated all complications after vaccination Variations in BCG potency have been reported but the introduction of freeze dry technics has allowed complete standardization regarding viability potency sterility and safety before distribution The vaccine can be stored up to 4 years In carefully conducted and controlled experiments there can be little doubt that BCG affords substantial protection against tuberculosis

The tuberculin test is lost as a diagnostic measure after BCG vaccine has been injected However an 80% reduction *in the incidence of tuberculous disease in vaccinated persons* as suggested by the British study more than compensates for the loss of the tuberculin test The tuberculin test is not paramount Various laboratory tests including sedimentation rates and x rays are also considered

Persons with negative reactions have a choice of BCG or chemoprophylaxis The vaccine is preferable because it raises the patient s immunity to tuberculosis its effect lasts for several years and it is effective without further co-operation by the patient Chemoprophylaxis does not raise immunity of itself it suppresses tubercle bacilli only while the drug is

*(1) J.A M A 164 951 954 J 29 1957*

mained normal in 45 patients and evidence of infiltration appeared in 21 in 19 as diffuse bilateral mottling in the mid zone and in 2 as small transient subsegmental shadows In 6 infiltration increased and in 3 became severe fibrosis The pulmonary shadows and enlarged nodes regressed completely in 12 of the 21 patients

Of the 66 patients 45 eventually had normal chest films 33 within a year of discovery of the disease and most of these in the first 3 6 months The longest time for the others was

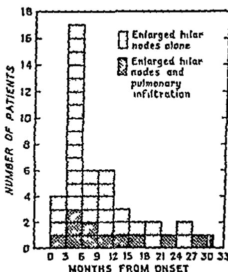



Fig 38 – Durat n of at rmal x r y n 45 p t ents. (Courtesy of Smell H and Hoyle C Lanc t 2 66- 0 July 13 195 )

31 months (Fig 38) The time required was much the same for those with pulmonary infiltration as for those with only enlarged nodes

Apart from ocular complications in patients with uveitis the clinical course was surprisingly uneventful Of the 66 patients 60 kept well Six became dyspneic because of diffuse pulmonary sarcoidosis which did not resolve Bilateral enlargement of the hilar lymph nodes is characteristic of early sarcoidosis *is harmless in itself and has an excellent prognosis* Treatment is required only for some associated lesions of which uveitis and persistent pulmonary infiltration are the most important

vaccinated person may have contributed to the resistance Present information is inadequate

BCG is as safe as any vaccine in common use though several cases of progressive disease and death have been reportedly attributed to it Since BCG converts nonreactors into reactors to tuberculin the tuberculin test becomes useless as evidence of recent infection as an index of infection in population groups for location of sources of contagion as a preliminary screening device before chest x ray examination or in differential diagnosis of diseases similar to tuberculosis These considerations are of increasing importance since the incidence of infection is declining and the hazards of excessive x radiation are of increasing concern If the protection afforded by BCG were absolute and persistent loss of the tuberculin test would be outweighed by the protection afforded However all studies indicate protection is imperfect and the loss of the index value of the tuberculin test becomes significant

A striking finding in all extensive studies is the high subsequent incidence of tuberculosis morbidity in persons strongly sensitive to tuberculin at the time of the survey who thus were ineligible for vaccination and therefore not in either the vaccinated or the control group In community studies in Georgia and Alabama no difference was demonstrable in the tuberculosis developing among vaccinated and nonvaccinated tuberculin negative persons observed 6 years. The tuberculosis which developed among those eligible for vaccination was an extremely small fraction of the total tuberculosis problem of the community during the follow up period

The potency of different BCG strains by laboratory tests and large field trials apparently varies markedly Critical analyses were made on only a small number of the lots used and various research groups differ on their choice of BCG strains for vaccination The label BCG does not define a product of predictable and standard properties and activity

In public health tuberculosis mortality rates for the white population in the United States few of whom receive BCG is similar to the mortality rates in European countries in which vaccination has been widespread The mortality in certain European countries of comparable size and economic

taken, it is experimental and requires continued patient co operation for many months

Negative reactors to the tuberculin test among highly ex posed persons—nurses medical students and children in families with tuberculosis—should have BCG vaccination and revaccination at suitable intervals to maintain as high a level of immunity as possible

► [The following report by another committee details the principal rea sons why BCG vaccination has not been accepted in this country for mass immunization and why it is not recommended except for limited use in certain special risk groups —Ed.]

**Report of Ad Hoc Advisory Committee on BCG to Sur geon General of United States Public Health Service** Rene J Dubos Herman Hilleboe Horace L Hodes Walsh Mc Dermott Gardner Middlebrook Rufus Payne James E Per kins Leon H Schmidt Jacob Yerushalmy and Esmond R Long[2] formulated a statement

All aspects of the tuberculosis problem have changed in the past decade mortality has decreased from 30/100 000 to 10/100 000 and the morbidity has also declined markedly The consequences of tuberculosis morbidity have become less because antimicrobial agents are effective particularly isoniazid The infection rate reflected in many tuberculin *testing surveys has reached a new low probably less than* 0 5% of the United States population are being infected each year and the risk of infection is decreasing at an accelerating rate

The basic premise of BCG vaccine is protection against the hazards of tuberculosis infection No benefit accrues to persons already infected Protection provided by vaccination apparently wanes in time therefore ideally only nonreac tors should be vaccinated within a few months before ex posure However tuberculous disease is more likely to de velop among persons who reacted positively to tuberculin testing and chief attention should be directed to them

The value of BCG has been controversial Several studies are convincing that vaccination in man with a strain of BCG of high potency increases resistance to tuberculosis The duration of resistance is undefined but several investigations suggest some protection for several years *In such groups* subsequent small spontaneous infections overcome by the

(2) Am R v T be c 76 726 731 No mbe 1957

lymphadenopathy developed and 4 consistently had positive gastric cultures All 8 had been receiving placebo

In untreated children under age 1 the risk of developing tuberculous complications was greatest with rate of 33/1 000 for those with normal roentgenograms 100/1 000 for

EXTRAPULMONARY COMPLICATIONS OF PRIMARY TUBERCULOSIS OCCURRING AMONG 1,394 CHILDREN RECEIVING ISONIAZID AND 1 356 RECEIVING PLACEBO

| Type of T berculous Compl ion | F rst 12 Mon hs | | Se nd 17 M h | |
|---|---|---|---|---|
| | Iso d | Placebo | Isoniazid | P bo |
| M n g t | 1 | 6 | — | 1 |
| Tube ul m | — | 2 | — | — |
| M i y d as | | 1 | — | 1 |
| Sk l t l d sease | 1 | 5 | 2 | 1 |
| I t pl l effus o | 1 | 7 | — | — |
| T ll ol ment | — | 1 | — | — |
| C j n i v t | — | 1 | — | — |
| Cl cally ll | — | 3 | — | — |
| T t l | 5 | 76 | 2 | 3 |

I q to bl d agn l n t t k g p lls

those with hilar or paratracheal involvement and 182/1 000 for those with parenchymal involvement Children between ages 1 and 6 were at little risk unless their roentgenographic findings were positive The only 2 children over age 6 who had complications were adolescents with initial parenchymal involvement in whom tuberculous pleurisy with effusion developed Treatment with isoniazid 4 6 mg /kg greatly reduced incidence of complications

► [It is important to differentiate this kind of prophylaxis which consists of treating primary infection whether clinically overt or manifested only by development of tuberculin allergy from attempts at chemoprophylaxis by administration of isoniazid before infection ha taken place (see next paper)

This demonstration of the valu of treating primary tuberculosis in childhood confirms on a large scale what has been previou ly demonstrated in stud es of smaller groups (see Robinson and Meyer 1957 58 YEAR BOOK p 179) and what has for several years been standard practice in many clinics —Ed ]

**Antituberculous Chemoprophylaxis with Isoniazid Preliminary Note** is presented by A Omodei Zorini[4] (Rome Univ ) Results have been striking in miliary tuberculosis and tuberculous meningitis treated with 20-40 mg isoniazid/kg These doses are well tolerated by children and are

(4) D Chest 33 1 17 J y 1958

state have been similar whether or not BCG vaccination was used

√The use of BCG should be determined by the particular circumstances in a local community Responsible officials should be apprised of the advantages and disadvantages of its use Large scale BCG vaccination is not indicated in this country In certain groups the advantages of vaccination outweigh the disadvantages for tuberculin negative persons exposed to a definite risk of infection especially if they can not be frequently retested with tuberculin These include physicians nurses medical and nursing students laboratory workers and hospital employees persons unavoidably ex posed to continued contact with infectious tuberculosis in the home and patients inmates and employees of institutions such as mental hospitals and prisons where exposure is likely to be great

**Prophylactic Effects of Isoniazid on Primary Tuberculosis in Children Preliminary Report** A United States Public Health Service Tuberculosis Prophylaxis Trial is reported by Shirley H Ferebee Frank W Mount and Anastasios A Anastasiades[3] The strictly controlled study which included placebos was to test the efficacy of isoniazid in prevention of postprimary complications and not the effectiveness of the drug in treating the complications Each child was given a prescribed number of pills daily for 12 months and was examined each month Isoniazid was given in daily doses of 4 6 mg /kg body weight The study was limited to asymp tomatic primary tuberculosis in children under age 3 with reaction of at least 5 mm to intermediate dose of tuberculin (5 TU) In children over age 3 x ray evidence of primary tuberculosis had to be present When treatment was required the child was excluded from the study

Among 2750 children observed by 32 clinical investiga tors serious extrapulmonary tuberculous complications de veloped in 5 taking isoniazid and in 26 taking the placebo (table) This is a significant difference indicating that iso niazid prevented 80% of the complications of childhood tuberculosis Adverse pulmonary changes less serious oc curred in 21 children who received isoniazid and in 34 who received placebo Incidence of lymphadenopathy and posi tive gastric cultures could not be compared but in 4 children

(3) Am Rev T bc c 6 94 963 December 1957

quate to evaluate the effects therapy had continued for 4 months in 300 patients and 2 months in 300

Isoniazid prophylaxis exerts immediate therapeutic action against existent tuberculous foci and furnishes greater resistance against endogenous or exogenous reinfection Treatment probably should be repeated at intervals during the 2d and 3d years especially if the patients are infants born of tuberculous parents

► [Dr Zorini Director of the Forlanini Institute in Rome has rather boldly attempted clinical chemoprophylaxis by treatment not only of the tuberculin reactors but of the nonreactors as well. This approach is based on the well known experiments of Ferebee and Palmer in which a high degree of protection against tuberculous infection by isoniazid chemoprophylaxis was demonstrated in guinea pigs This preliminary note inso far as it relates to chemoprophylaxis of the nonreactors reports no results which would permit evaluation of this as an alternative to BCG vaccination or as a practically feasible method of tuberculosis prevention The experience so far as it has gone does illustrate, however some of the practical difficulties to be expected were a program of mass chemoprophylaxis to be undertaken The subject is included here mainly because some physicians are already undertaking to treat with isoniazid family contacts *who are nonreactors* a procedure which is certainly *not established* as standard practice. Much more work will be necessary before it becomes known whether this is a reliable and a safe method of prevention —Ed.]

**In Vitro Action of Antituberculous Agents Against Multiplying and Nonmultiplying Microbial Cells** Studies of many types of antibiotics have shown them to be most effective against susceptible microbes when actively multiplying Bacteria that actually are susceptible to the antibiotic may appear resistant to it in vivo because the drug cannot act on slowly metabolizing dormant or nonmultiplying cells

Gladys L Hobby and Tulita F Lenert[5] (Brooklyn) inoculated strains of Mycobacterium tuberculosis into a Tween® albumin liquid medium containing various concentrations of streptomycin isoniazid and viomycin singly or in succession and incubated at 37 C for 12 14 days Results were remarkably similar to those obtained with penicillin and strains of Streptococcus hemolyticus The log of the number of survivors plotted against time followed a straight line downward until 99% were killed With streptomycin the last 1% of tubercle bacilli continued to decrease remained stationary or even increased The period during which about 99% of the organisms were destroyed paralleled the period during which the total number of organisms in absence of streptomycin increased along a straight line Almost iden

(5) Am R T berc 76 1031 1048 Dec mbe 1957

bacteriocidal The observations suggested that this treatment be used for skin positive subjects and to sterilize the infected organism thus avoiding the clinical evolution of tuberculous disease Therefore 20 patients aged 12 20 with *node pulmonary tuberculosis received 20 mg isoniazid/kg* daily for 150 days Degree of pathology varied from minimal to severe with wide extension and destruction of the pulmonary parenchyma

Clinical results after 5 months of therapy appeared favorable in 17 with local systemic and radiologic improvement Weight increased in 60% sedimentation rate decreased in 75% and skin reactivity to tuberculin increased in 6 decreased in 5 and was unchanged in 9 Circulating antibodies increased in nearly all Among 5 with positive cases sputum and gastric cultures became negative in 3

Since the drug is well tolerated 20 mg/kg/day is indicated for children and young people In newborns and children up to age 3 15 20 mg/kg/day is indicated especially in the acute progressive phases In grown children and young adults 8 12 mg/kg suffices

*Over 600 children aged 4 11 from families with tuberculosis* who showed positive skin tests but no clinical or radiologic manifestations of active tuberculosis *received 20 mg isoniazid/kg/day* for 6 months About 40% remained at home Most of these were from healthy families but some lived with tuberculous or extuberculous persons The other 60% were sent to sanatoriums Another 600 children in the same environmental conditions were left untreated The therapeutic program was much more difficult in patients treated at home It was difficult to convince relatives of these asymptomatic patients to permit the children to have diagnostic procedures

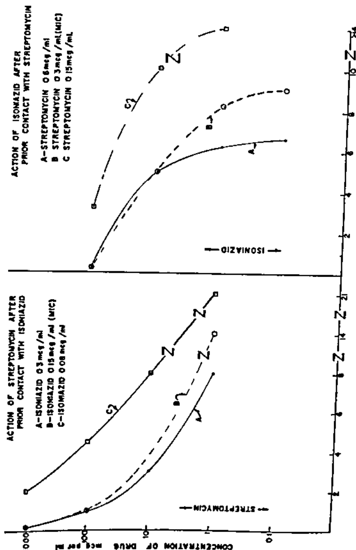
Isoniazid was started with 10 mg/kg/day and was increased by 5 mg/kg/day weekly until a dose of 20 mg/kg/day was attained Drug tolerance was excellent Only 4 of the 600 had to discontinue treatment 2 because of relapsing dermatitis and 2 because of gastroenteritis Weight increased in nearly all

Prophylactic treatment with high doses of isoniazid is possible in tuberculin positive or negative persons without specific active pulmonary lesions Follow up is as yet made

The proportion of cells resistant to the antibiotic did not increase during incubation The rate of killing increased within limits as concentration of the drug increased When isoniazid was given first followed by streptomycin or vice versa the higher was the concentration of the initial drug used and the lower was the concentration and/or time required for subsequent destruction of surviving organisms by the second drug (Fig 39) Many antimicrobials streptomycin oxytetracycline neomycin polymyxins A and B viomycin and others act primarily at time of cell division Suspending tubercle bacilli in nonnutrient medium interferes with streptomycin action and this antimicrobial has little bactericidal activity against resting cells The same is true of isoniazid This phenomenon may be universal applying to all antimicrobial drugs The ability of antimicrobial drugs to act only at time of cell division imposes an important limit to their use and is especially important in vivo

The significance of these facts with respect to mode of action of antituberculous drugs is yet unknown If 1% tubercle bacilli survive many of the organisms remain viable If the host defense mechanisms cannot eliminate these residual cells a second drug may be advantageous Repeated destruction of 99% of the surviving population by a series of successive drugs could nearly eradicate the infection Much higher drug concentrations are required to eradicate essentially all rather than a small proportion of the population Those that survive after only a small part is destroyed multiply faster Inhibition of cell multiplication and actual killing of the micro organisms may occur through two separate mechanisms Perhaps the antimicrobial drugs delay and/or prevent cell division whereas when bactericidal effects ensue they may be only indirect results of antimicrobial action

**Effect of Pyridoxal on Uptake of $C^{14}$ Activity from Labeled Isoniazid by Mycobacterium Tuberculosis** Isoniazid competes with vitamin $B_6$ in the formation of indole by Escherichia coli and the inhibition of several micro organisms by isoniazid has been reversed by the use of pyridoxine and its derivatives This effect has been noted in vitro with M tuberculosis H37Rv Since it is known the hydrazine group of isoniazid may react with a ketone group this ketone group may be involved in neutralizing the antituberculous effects of isoniazid Irene U Boone Verda G Strang and




F g 39 —Effect f ent at on of i n a d or st pt y n c nc t ti n a d/ t me qu r d f bse qu t d truct n by st ept my n so d pect ly f 99% f ll rvi g t m t 1 t n f drug sed t lly (C rtesy of H bby G L d Le ert T F Am R v T be 76 1031 1048 Dec mbe 1957)

tical curves were obtained with isoniazid viomycin and oxytetracycline The results suggested that nonmultiplying cells might be insusceptible to the action of these agents

When many organisms were inoculated multiplication did not occur and the antibiotics had no antimicrobia ffect

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Betty S Rogers[6] (Univ of California) measured the uptake of isoniazid by mycobacterium in the presence of reported antagonists (Fig 40) Cellular uptake was increased by the presence of pyridoxal

Growth of M tuberculosis H37Rv is inhibited by isoniazid and this inhibition is reversed in the presence of pyridoxal A weak solution of isoniazid dissociates to isonicotinic acid

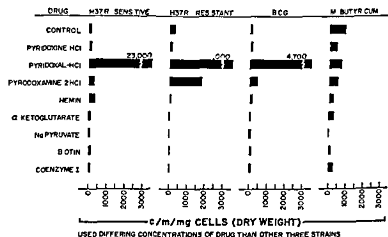



Fig 40—Uptake of C act ty in presence of report d a t go ists of so iazid (C t y of B I U et al Am R Tuberc 76 568 578 October 1957)

When pyridoxal and $C^{14}$ isoniazid are added to distilled water or culture medium all $C^{14}$ activity appears as isonicotinic acid Pyridoxal may act as an accelerator of this dissociation but most likely serves as a receptor for the dissociated amine group subsequently forming pyridoxamine The isoniazid may act similarly to the amino acids participating in transamination reactions

The isoniazid or $C^{14}$ activity bound by the cells seems to be a physical adsorptive process rather than an ordinary chemical reaction *Increased cellular uptake of $C^{14}$ activity* from labeled isoniazid in the presence of pyridoxal may be due to a change in cell adsorptive properties and/or a change in the sites at which the material is bound Nearly all the $C^{14}$ activity on the cell can be removed at pH 3-4 in

(6) Am R T be c 76 568 578 Octobe 1957

dicating that binding is not as firm as the fixing of radiopenicillin by various bacteria

The interaction of pyridoxal and isoniazid apparently is unaffected by the presence or absence of tubercle bacilli Chromatographic studies of this interaction demonstrated no pyridoxal isonicotinoyl hydrazone Solutions containing this compound were unstable dissociating rapidly to isonicotinic acid pyridoxal and a trace of isoniazid which probably explains its in vitro inhibition of susceptible strains of M tuberculosis The mode of action of isoniazid is still unknown

[This and the following paper by McCune *et al* suggest that, contrary to reported clinical impressions the concurrent administration of pyridoxine may appreciably antagonize the antituberculous effect of isoniazid An important practical question is therefore whether the administration of pyridoxine to permit higher dosage of isoniazid, without attendant excessive risk of neuritis may not neutralize at least in part, the desired *therapeutic advantage of the higher isoniazid concentration*

The antagonism of isoniazid and pyridoxine or its derivatives was first reported as early as 1952 and attempts have been made to explain the mode of action of isoniazid on M tuberculosis on this basis However as has been pointed out by Albert (*The Strategy of Chemotherapy* Cambridge University Press 1958 p 132) this antagonism explains more about the toxic side effects than it does about the therapeutic action of the drug which he believes is in large part through chelation of heavy metal ions —Ed.]

**Delayed Appearance of Isoniazid Antagonism by Pyridoxine in Vivo** Large doses of isoniazid can reduce the population of tubercle bacilli in tissues of mice even though some pyridoxine is given concurrently for as long as 84 days However in vitro pyridoxine may reduce the antimicrobial effectiveness of the isoniazid To test this antagonism in vivo Robert McCune Kurt Deuschle and Walsh McDermott[7] (New York Hosp Cornell Univ Med Center) inoculated large numbers of mice intravenously with tubercle bacilli of the H37Rv strain and administered doses of 0 0125 and 0 003% isoniazid and 0 0015 and 0 036% pyridoxine in the diet Small groups of mice were killed at planned intervals and the populations of tubercle bacilli determined in the lungs and spleens

The large doses of pyridoxine when given with the large doses of isoniazid antagonized the antituberculous effect of isoniazid during the last 2 months of the 3 month experiment No antagonism was observed when smaller doses of pyridoxine were administered with smaller doses of isonia

(7) Am Rev T berc 76 1100 110 Decembe 1957

zid The results support the hypothesis of a direct pyridoxal isoniazid reaction previously demonstrated in vitro

The total isoniazid available for antimicrobial purposes in a particular patient cannot be assumed to remain uninfluenced by the concomitant administration of pyridoxine Pyridoxine may be indicated in clinical practice and it may be important to prevent pyridoxine deficiency in patients receiving isoniazid Perhaps very large doses of free isoniazid can be made available in the tissues with safety provided the tissues have received sufficient pyridoxal Nevertheless it is possible that the neuritis preventing effect of pyridoxine administration is simply the reduction of free isoniazid available for both therapeutic and toxic effects within the animal

**Effect of Certain Aromatic Amines on Serum Isoniazid Concentrations in Tuberculous Patients** Isoniazid is so rapidly metabolized by some persons that serum concentrations of active drug may be too low to measure a few hours after administration of a test dose though significant amounts exist in biologically inactive forms The most abundant metabolite is the acetylated form and as much as 60% of an administered test dose may be excreted in this form J Carroll Bell D K Riemensnider and Roger S Mitchell[8] (Univ of Colorado) administered isoniazid with each of several aromatic amines which are metabolized by acetylation to determine whether these might reduce the rate of isoniazid acetylation

Biologically active isoniazid was measured by microbiologic assay in 20 patients with tuberculosis after isoniazid was given alone and again after it was given simultaneously with PAS PABA (para aminobenzoic acid) sulfanilamide and sulfadiazine Serum concentrations of biologically active isoniazid were often elevated and prolonged by the simultaneous administration of these agents (Fig 41) The effect was obvious in most patients but some showed no such change Response to the sulfonamides was similar but less constant and often less marked than with PAS or PABA

Perhaps some treatment failures with isoniazid may be due at least in part to extensive metabolic degradation in some patients Some benefits of combined isoniazid PAS therapy may be due to the competitive metabolism allowing

(8) Am. Rev T berc 76 152 158 J ly 1957

more isoniazid to remain active Preliminary observations of the urinary excretion of isoniazid and isoniazid metabolites indicate that addition of these agents inhibits not only acetylation but also the further metabolism of isoniazid to isonicotinic acid and other conjugates As one metabolic

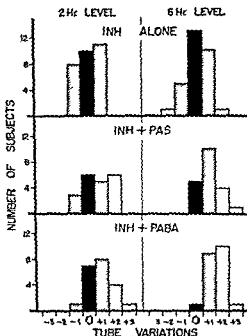



Fig 41 —S m lev l f b l g lly t d obta d 2 d 6 h aft t t g w th d l w th d PAS d w th so d PABA Uppe g ph how m m l t b y lt bt d on pe t d t t g w th so iazid alon 30 ubj e B ay lt bt d n t al t t g w tak f en p s f mp w th all ub q nt b y d t m t M ddl a d l w g ph k w m x m l t n n b ay ults bt d 20 tube u lou pat ent ult ft a d al w d s fe po t f m p so w th lt bt ed ft m lt dm t t f d nd PAS (m ddl graph ) d son d d PABA (l w g ph ) (C rt y f B U J C f Am R T be 76 152 158 J ly 1957 )

pathway is blocked secondary alternative pathways may be largely used Perhaps isoniazid dosage should be determined by the degree to which the drug is inactivated rather than by the milligram/kilogram formula currently used

**Endobronchial Tuberculosis in Children Study of 156 Patients** is presented by Edith M Lincoln Leonard C Harris

Somchai Bovornkitti and Rosaria W Carretero[9] (New York) Review of 1 000 children with primary pulmonary tuberculosis between 1930 and 1946 showed that the mortality rate was about 20% and that 95% of the deaths were due to meningitis miliary tuberculosis protracted hematogenous tuberculosis or local progression

The pressure syndrome of tuberculous nodes pressing on the tracheobronchial tree was frequently noted but was not often directly responsible for death One child suffocated after caseous material was extruded from lymph nodes into the trachea In a few fatal caseous pneumonia developed secondary to erosion of a caseous node through the bronchial wall Thus before antimicrobial therapy endobronchial tuberculosis was not often a cause of death However, permanent bronchial or pulmonary damage frequently follows endobronchial tuberculosis Incidence of bronchiectasis and lesser deformities of the bronchial tree is high

Between 1947 and 1954 156 children were found to have bronchoscopic evidence of tuberculous endobronchitis During the years of the study 65% of the total children's ward population was under age 4 compared with 83% of those with proved endobronchial involvement Ratio of boys to girls in the ward was 1 1 but among those with endobronchitis it was 94 60 Cough was the commonest symptom Wheeze dyspnea cyanosis and marked spasmodic cough were usual in the young infants

A controlled study was impossible At first streptomycin was given for only 6 weeks later for 6 months or more with PAS or sulfone Promizole® During the last 2½ years of the study isoniazid with PAS or sulfone was given usually for at least 1 year Cycloserine was tried in a few who did not respond to other therapy All patients with serious forms such as meningitis or miliary tuberculosis received specific therapy for 1 3 years In 70 patients in whom duration of endobronchitis could be measured antimicrobial therapy had no beneficial effect 40 received antimicrobial therapy for 6 months or over yet 33 had active endobronchitis 6 months to 3 years later and in some the local disease progressed during the period in which they were receiving treatment

Bronchograms obtained in 103 patients were normal in

(9) Am R T ber 77 39 61 J n ry 1958

33 minimally abnormal in 20 and markedly abnormal in 50 Frequency of abnormal bronchograms was the same whether the children were untreated or treated under or over 6 months Specific therapy did not prevent secondary damage to the lungs or bronchi Diagnosis of tuberculous endobron

Fig 4 —Bo hial t o ch ld ag d 3 B on h scopy A g 7 1947 h wed g lat on t n ght m ddl lobe nc d om t h l g 6 months End esult teno of ght m dd l be b hu Streptomycin and PAS g ven fo 3 month right m ddl lobe sect d Ja 12 1955 A x y on F b 10 195 howi g w den g of upper m d st m to ght and ea of t gula cloud g below 6th posteri ib on ight B late l w n same da n t a of cloud g c e pon i g to right m ddl lobe C x ay on A g 13 1953 n tic tung sten u f ight middl l be b on hu D ect n of ght m ddl lobe h w g ma kedly ct t b on h le f d f om ×25 (Co rtesy of L col E M t l Am Rev T be c 77 39 61 Janu ry 19 8 )

chitis can often be inferred in absence of symptoms because roentgenographic evidence of an obstructed segment or lobe is common (Fig 42) Endoscopy is probably the most reliable diagnostic measure

Tuberculosis of the bronchus in adults is usually due to

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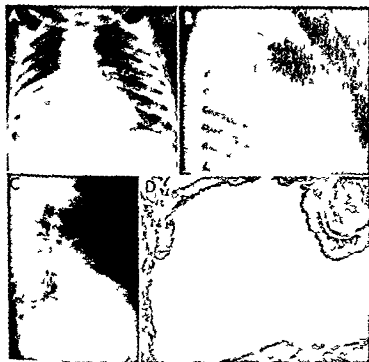



Fig 4 —B on hial tenos b ld g d 3 B on bosc p A g 194 h wed gra lat on t in right m ddl lobe fi d on t heali g 4 month End esult stenos f ght m ddle lobe b h St ptomy in d PAS en f 3 month right m ddle lobe esect d J 31 19 5 A x y on F b 10 19 h wing widen g f ppe m d t m to ght d ea f t ia gula l d g below 6th post ri rib on ght B lat l ew sam dat os f loud g corr pond g to right m ddl lobe C x on A g 13 1953 d t g sten is f ght middl lobe b on h D sect on f ght m ddl l be h w g ma k dly et r b on h fe ed d f om x 25 (Courtesy f L col E M r J Am Rev T be c 77 39 61 January 1953 )

chitis can often be inferred in absence of symptoms because roentgenographic evidence of an obstructed segment or lobe is common (Fig 42) Endoscopy is probably the most reliable diagnostic measure

Tuberculosis of the bronchus in adults is usually due to

contamination of the mucosal lining of a bronchus by sputum containing large numbers of tubercle bacilli usually from an adjacent cavity Ulceration begins in the mucosa and may heal rapidly with specific therapy The antimicrobial agents usually reduce the tubercle bacilli in the adjacent cavity and prevent relapse or reinfection

In children tuberculous endobronchitis is due to encroachment of enlarged nodes on the trachea or bronchi The nodes become fixed to the bronchial walls by inflammatory changes and the infection progresses through the walls of the bronchi to the mucosal lining ultimately creating the specific ulceration or granulation tissue by which a positive diagnosis is made by bronchoscopy The granulation tissue may ultimately form polyps which may persist for months and often recur if removed surgically A caseous node may erode the bronchial wall and form a sinus through which caseous material is extruded

Surgery should always be considered in children with endobronchial tuberculosis if there are extensive areas of bronchiectasis especially in the middle or lower lobes and obviously airless segments especially in the right middle lobe lingula of the left upper lobe or in the apical segment of either lower lobe or if there is definite marked narrowing or stenosis of a bronchus A large amount of calcium within an obstructed area is a clear indication for surgery as such areas usually contain caseation and active tuberculosis Antimicrobial therapy does not shorten the course of endobronchial involvement in children or decrease incidence of sequelae but treatment is indicated to diminish the dangers of bronchogenic spread ✓

**Hospital Treatment of Pulmonary Tuberculosis Follow up Study of Patients Admitted to Edinburgh Hospitals in 1953** J D Ross N W Horne I W B Grant and J W Crofton[1] followed 156 males and 149 females with pulmonary tuberculosis for 3-4 years On admission 251 (82%) had positive sputum laryngeal swabs or gastric lavage Of the 305 patients 190 were sensitive to streptomycin PAS and isoniazid 30 were resistant to 1 drug 19 were resistant to 2 drugs 8 were resistant to all 3 drugs and 4 were undetermined All but 7 received chemotherapy Of the 7 1 had thoracoplasty because of bacilli resistant to PAS and isoni

(1) Brit M J 1 237 242 Feb 1 1958

azid 1 because his disease was thought to be inactive and 5 who were moribund on admission died without receiving drugs The usual drug therapy was streptomycin 1 Gm daily plus PAS 5 Gm 4 times daily streptomycin 1 Gm daily plus isoniazid 100 mg twice daily isoniazid 100 mg twice daily plus PAS 5 Gm 2 or 4 times daily or a combination of all 3 drugs In some streptomycin was given 2 3 times weekly and PAS daily This practice was abandoned because it car

TABLE 1—OUTCOME OF TREATMENT RELATED TO USE OF MAJOR CHEST SURGERY AND SENSITIVITY OF ORGANISMS TO 3 STANDARD DRUGS IN HOSPITALIZED PATIENTS

| State at Discharge | Later Fate | Patient Having | | | | | | Totals | |
|---|---|---|---|---|---|---|---|---|---|
| | | Organism Sensitive to at Least Two Drugs | | | Organism Resistant to at Least Two Drugs | | | | |
| | | Major Surgery | No Surgery | All Cases | Major Surgery | No Surgery | All Cases | | |
| Sputum negative | Remaining well | 95 | 131 | 2 6 | 13 | 1 | 14 | 40 | 64 |
| | Relapse | 2 | 13 | 15 | 3 | 0 | 3 | 18 | |
| | Death (all causes) | 0 | 5 | 5 | 1 | 0 | 1 | 6 | |
| Sputum positive | Still positive | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 7 |
| | Lost sight of | 0 | 1 | 1 | 0 | 0 | 0 | 1 | |
| | Now negative and well | 0 | 4 | 4 | 1 | 0 | 1 | 5 | |
| | Death (all causes) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Died in hospital (all causes) | | 3 | 16 | 19 | 3 | 8 | 11 | 30 | |
| Still in hospital | | 0 | 0 | 0 | 0 | 4 | 4 | 4 | |
| Totals | | 100 | 170 | 270 | 2 | 13 | 35 | 305 | |

ries the danger of the patient s organisms becoming resistant first to PAS and then to streptomycin Major thoracic surgery was done in 122 patients including thoracoplasty pneumonectomy or resection of lobes segments or emphysematous portions of lung Thirty patients died in the hospital 271 were discharged and 4 are still hospitalized 3 years later Six died later of unrelated diseases Of the 271 who were discharged 7 (2 6%) had positive sputum Table 1 summarizes the results Among 20 patients in whom death was directly attributable to tuberculosis in 15 death was due to progression without any other condition congestive failure

developed in 1 severe emphysema in 1, amyloidosis in 2 and hemoptysis in 1

Of the 264 patients discharged with negative sputum in 18 (7%) relapse occurred in 16 as deterioration of the lung condition Of these 16 patients reversion to positive sputum developed in 13 Six patients had taken discharge against advice 2 of whom relapsed Resistance to 2 or all 3 drugs was present at time of relapse in 4 patients and 3 of these had been known to have resistant organisms while hospitalized

Among 22 patients operated on who had resistant organisms 4 died and 16 were discharged with sputum negative but 3 of these relapsed Of the 13 patients with resistant organisms who were not operated on only 1 was discharged *with sputum negative and 8 died of tuberculosis Of 100* patients who had drug sensitive organisms and were operated on 97 were discharged with sputum negative only 2 of these relapsed Of the 144 patients who were not operated on and discharged with sputum negative 13 relapsed

A survey of 269 patients 3 4 years after admission (Table 2) showed only 3 4% were unfit for work as a direct consequence of tuberculosis

The main factors contributing to death from tuberculosis was delayed admission and drug resistance both factors are preventable The relapse rate of 7% among survivors is still unsatisfactorily high and drug resistance is an important factor In patients with drug sensitive organisms the most important single factor in reducing risk of relapse was the duration of chemotherapy No relapse occurred in patients receiving more than 15 months of chemotherapy Those who had drug resistant infections did better when operated on

Previously untreated patients who are hospitalized are now treated with all 3 standard drugs Newer drugs should not be substituted for the standard drugs until careful trials have proved them to be adequate Even patients with minimal disease receive uninterrupted chemotherapy for at least a year and usually for a year after sputum conversion cavity closure or operation whichever is last In severe disease treatment continues for at least 2 years Desperately ill patients are treated with corticosteroids in addition to chemotherapy Cavities that fail to close on chemotherapy usually

are resected unless risk is too great Totally destroyed lungs extensive bronchiectasis and narrow stricture of lower lobe bronchus are definite indications for resection Surgery is most important in patients who have drug resistant organisms because of previous unsatisfactory chemotherapy

Nearly all patients who are newly diagnosed as having pulmonary tuberculosis should recover and 100% success is not an unreasonable goal Failure can almost always be traced to errors committed by the doctor or the patient the doctor failing to prescribe reliable combinations the patient failing to take them as prescribed Failure should not be accepted with complacency but an explanation should be assiduously sought

TABLE 2—Survey of 269 Patients 3-4 Years after Admission

| | No of Patients | |
|---|---|---|
| Fit for work | | |
| Working or normal retirement | 243 | 250 (93%) |
| Unemployed | 7 | |
| Unfit for work because of tuberculosis | | |
| At home | 5 | 11 (4%) |
| In hospital | 6 | |
| Unfit owing to nontuberculous disease | | 8 (3%) |

**Ambulatory Treatment of Patients Hospitalized with Pulmonary Tuberculosis** The use of ambulation exercise or bed rest in treating tuberculosis has been debated for nearly a century Since the advent of modern chemotherapy nearly all hospitals in the United States have liberalized bed rest restrictions To evaluate the role of bed rest in the treatment of tuberculosis James A Wier Robert L Taylor and Richard S Fraser (Fitzsimons Army Hosp Denver) assigned at random 203 patients who had moderately or far advanced pulmonary tuberculosis to modified bed rest or free ambulation All received the same regimen of chemotherapy streptomycin or streptoduocin 2 Gm every 3 days for 6 months then 1 Gm every 3 days for the duration of hospitalization isoniazid 10 mg/kg daily and PAS 12 Gm daily No patient had received prior treatment

The modified bed rest program was fairly strict bed rest for 3 months with one bathroom privilege daily and meals at bedside then free bathroom privileges and 4 hours daily

(2) Ann I t M d 47 762 773 O tobe 1957

out of bed When x rays showed the disease had become stabilized and the sputum had converted patients were allowed out of bed for increasing periods and allowed short passes several times a month Two bed rest periods of 2 hours each morning and afternoon were strictly enforced The ambulatory group were given complete freedom from the first day of hospitalization They were not prohibited rest in bed but efforts were made to keep them active

All 108 patients with minimal pulmonary tuberculosis did well regardless of activity Sputum converted soon after chemotherapy was started Similarly in patients with pleural effusion no demonstrable difference could be seen in the ambulant and rest groups all did equally well Of the 203 patients 5 in the ambulatory group and 3 in the bed rest group were worse as measured by an enlarging single cavity at either 120 or 180 days and each did well after surgical resection of the open cavity at 180 days At the end of 8 months of treatment all patients in both groups were bacteriologically negative and as a group little difference was evident in the degree of x ray improvement or cavity closure

This study shows that liberalization of bed rest requirements in patients with pulmonary tuberculosis was not harmful The advantages are many Less general nursing care is required the patients care for themselves straighten their rooms clean their own bedside areas pick up their own trays and eat at table Educational and recreational programs are easier to administer as group activities In general morale is much higher in the ambulant group

► [Interest is shifting in tuberculosis therapy from the comparative evaluation of different drug regimens to attempts such as this of Wier and his associates to estimate the value of physical rest in the therapeutic program How radically concepts have changed is illustrated by the fact that long term physical rest which was so long the basic measure of therapeutic management has come to be regarded as an ancillary measure of doubtful added value when patients are receiving the benefits of effective antimicrobial therapy From ambulatory treatment of hospitalized patients to the treatment of patients at work is a logical step That this can be done successfully in *selected* patients is convincingly shown in the following report by the Research Committee of the Tuberculosis Society of Scotland —Ed ]

**Treatment of Pulmonary Tuberculosis at Work Controlled Trial** An interim report by the Research Committee of the Tuberculosis Society of Scotland is presented by D T Kay[3] Of 115 patients studied 58 were allocated at random

(3) Tube 1 38 375 381 1957

to the bed rest group and 57 were at work None had a cavity more than 2 cm in diameter and the sputum of each was negative for tubercle bacilli by direct smear Patients under age 15 non Europeans pregnant women and those within 3 months of parturition diabetics and patients previously treated by chemotherapy or collapse therapy were excluded from the study

Patients in the group at work continued to lead a normal working life throughout Those in the control group were confined to bed at home or in a hospital for at least the first 3 months and were allowed up to toilet only Bed rest could be continued beyond 3 months at the physician s discretion Both groups received 5 Gm PAS plus 100 mg isoniazid twice daily for a minimum of 6 months The two groups were similar as to age sex occupation and x ray classification of disease

The initial evaluation showed that with suitable chemo therapy in the less severe forms of pulmonary tuberculosis patients who were allowed to work did as well as those treated with bed rest Treatment of patients at work is not simple The patient may not fully appreciate the potential seriousness of the condition and may fail to take the pre scribed chemotherapy This is common Failure to take ade quate chemotherapy may lead to relapse In choosing to treat a patient at work one must assess how co-operative the patient will be The patient must be impressed with the vital necessity for strict compliance with the treatment regimen and be told to make every effort to take the drugs as pre scribed The treatment of pulmonary tuberculosis at work should be confined to highly co-operative patients with mild disease who are unlikely to be a source of danger to their fellows Facilities must be available for close supervision

Prednisolone in Treatment of Pulmonary Tuberculosis Controlled Trial A preliminary report is presented by the Re search Committee of the Tuberculosis Society of Scotland[4] Early clinical reports and experiments in animals stressed the enhancing effect of steroid hormones on tuberculosis Re cent reports suggest a therapeutic effect To assess the func tion of corticosteroids 90 cases were selected at 7 medical centers to conform to the following criteria anticipation of at least 6 months hospitalization without surgery or col

(4) Brit M J 2 1131 1134 N 16 1957

lapse therapy no previous collapse therapy or chemotherapy *no extrapulmonary disease no pregnancy over age 15 no* other condition that would contraindicate use of corticosteroids and no tubercle bacilli known to be resistant of streptomycin PAS or isoniazid Each patient was allocated to a subgroup of acute chronic or chronic with acute spread

Each patient was assigned randomly to one of two treatment groups All received bed rest for 3 months The control group (46 patients) received chemotherapy only those under age 40 received 1 Gm streptomycin a day and 100 mg isoniazid twice a day those over 40 received 1 Gm streptomycin thrice weekly 5 Gm PAS twice a day and 100 mg *isoniazid twice a day The treatment group (44 patients)* received chemotherapy as in the control group 5 mg prednisolone 4 times a day for 3 months 30 units of ACTH gel intramuscularly on 2 successive days every fortnight for 3 months and 2 Gm potassium citrate twice a day for 3 months

Clinical improvement was more rapid especially in acutely ill patients in the group treated by prednisolone The erythrocyte sedimentation rate fell more rapidly in this group Radiologic improvement was significantly hastened over the 6 months and most of the improvement occurred in the first 2 months Cavity closure and sputum conversion were slightly hastened by prednisolone but the difference was not significant No patient receiving prednisolone showed any deterioration though a temporary rebound phenomenon was observed radiologically in 7 of the 44 No serious side *effects were noted Prednisolone therapy may be indicated* in patients severely ill with pulmonary tuberculosis Toxic symptoms are rapidly abated

**Formation of Bullous Cavities Following Antimicrobial** ***Therapy for Pulmonary Tuberculosis*** A A *Weiner and* V Boldowsky[5] present 4 cases of far advanced bilateral caseous pneumonic and cavernous pulmonary tuberculosis which healed with chemotherapy but subsequently showed new bullous and cystlike cavities *Before* antibiotic *therapy these* were not found but especially since the introduction of isoniazid the condition has become more frequent

With the advent of chemotherapy the incidence of bronchopulmonary suppurative processes has decreased *where*as bullous and cystic changes have increased In pulmonary

(5) Sea V w H p Bull 14 170 180 July 19 7

tuberculosis chemotherapy results in closing of cavities but newly formed cystlike cavities appear either abutting the site of the former cavity or close to it These new cavities have a thin outline appearing on x rays as emphysematous blebs A cavity wall is flexible thin and smooth without caseation and without macroscopic fibrous reaction These bullous cavities require no surgical or other treatment They are benign and bacteriologically sterile During antimicrobial therapy the cystlike cavities develop when the sputum is converted and clinical symptoms disappear Chemotherapy should be continued at least 2 years

► [The observations of Weiner and Boldowsky and those reported in the following paper by Tchertkoff Altmann and Nenashev (also of Sea View Hospital) emphasize the growing importance of attempting to differentiate clinically and roentgenologically between different types of residual lung cavities The Sea View Hospital group were among the first to point out the clinical significance of open healing of cavities and of the replacement of cavities by bullous cysts Their studies have given them more confiden than most clinicians have yet developed in the ability to recognize those lesions which do not require surgical resection —Ed ]

**Open Healing of Cavities in Pulmonary Tuberculosis Treated with Antimicrobials Clinical and Pathologic Study** is reported by I G Tchertkoff V Altmann and P Nenashev[6] Antimicrobial therapy can completely heal cavities and caseous or acinous nodose foci This can be observed in x rays and diagnosed clinically In some cases managed medically the cavity images by x rays may appear to be rapidly formed and rapidly healed tuberculous cavities or pneumatic cysts formed by rapid absorption of the exudative tuberculous process Regardless of the exact pathogenesis they are not active tuberculous lesions Diagnosis is easy once the cavities are recognized They appear and act like the pneumatoceles that follow rapid resolution of acute pneumonia in children In patients with tuberculosis they are usually seen in predominantly exudative lesions that resolve rapidly with isoniazid therapy

By x ray three types of cavities can be distinguished Some appear as highlights 0 5 1 5 cm in diameter which persist without noticeable change for the entire period of observation as long as 3 years They look like bronchiectasis except they are in the apexes replace small tuberculous cavities previously visualized in the same location are regular round and have a smooth inner contour Others appear as

(6) Sea V w H p B ll 14 147 169 J ly 1957

large cystlike formations frequently multiple with thin round smooth linear walls resembling large emphysematous bullae but in the middle of a lobe rather than the periphery or apex They may enlarge but usually get smaller and even disappear in a few months Fluid level is rare They



Fig 43—La ge c ity with regula fib t e w ll dest oy l ft upp r lole, c o n d f c) and fib o p ent n left l we J b H art a d m d st m d plac d to left S n e put m was alt t ly p t and n gat e fo 5 n ths ft pneu m ectomy a ty wa not ou ce f po t v put m (C urte y f Tche tkoff I G et l Se Vi w Ho p B ll 14 147 169 July 1957)

usually develop in patients in whom illness is recent and appear on x rays after rapid resolution of extensive exudative lesions In patients who have had resections the walls of these emphysema like formations are not lined by bronchial epithelium Encapsulated tuberculous foci may be found The third group of healed cavities are those usually located in the apexes often reaching the pleural surface They have finely delineated thin fibrotic walls and a regular inner contour

The mere presence of these cystic defects is not an indication for resection. Experience with 20 patients so affected followed for up to 4 years indicates that the patient with a sputum negative on smear and culture for 1 year or more and who shows the x ray criteria of a healed cavity has a healed lesion and needs no surgical intervention. None of the 20 patients had a relapse.

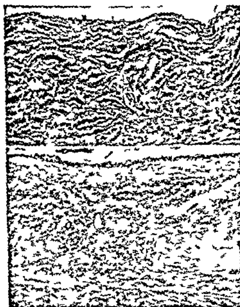


Fig 44 (top) —Cystic cavity under low power. Wall ... consists of dense fibrous tissue.
Fig 45 (bottom) —Cystic cavity under low power ... chronic inflammatory ... part of wall and part ... epithelization.
(Courtesy of Tchertkoff, I ... et al ... Sea View Hosp Bull 14 147 169 ... 1957)

Man 40 acquired tuberculosis in 1951 for which he was treated in several hospitals. In 1953 sputum was positive and he had extensive fibrocaseous and cavernous tuberculosis involving the entire left lung. The upper two-thirds was destroyed by a giant cavity. There was extensive bronchogenic spread from the hilus to the lower two thirds of the right side (Fig 43). He received streptomycin and isoniazid. Sputum was alternately positive and negative until 5 months after operation.

Pathologic examination showed marked pleural thickening and a cyst 12 14 cm in diameter occupying 75% of the upper lobe. The wall was dense fibrous tissue (Fig 44). Sections of large bronchi

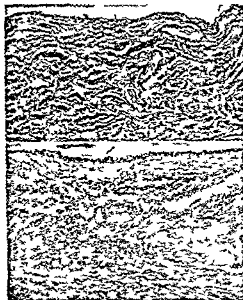
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Fig 43—L g c ty w th g l fib t wall dest oy l ft ppe l be, o- odous foc a d fib s s p t left l w l be H rt a d m d t m d pl ed t l ft S ce p t m wa lt rn tely po t d n g t e f r 5 n th after p eu m ectomy c ty w n t c f po t v p t m (Courte y f T h rtkoff J G t l S View Hosp B ll 14 147 169 J ly 1957)

usually develop in patients in whom illness is recent and appear on x rays after rapid resolution of extensive exudative lesions In patients who have had resections the walls of these emphysema like formations are not lined by bronchial epithelium Encapsulated tuberculous foci may be found The third group of healed cavities are those usually located in the apexes often reaching the pleural surface They have finely delineated thin fibrotic walls and a regular inner contour

The mere presence of these cystic defects is not an indication for resection Experience with 20 patients so affected followed for up to 4 years indicates that the patient with a sputum negative on smear and culture for 1 year or more and who shows the x ray criteria of a healed cavity has a healed lesion and needs no surgical intervention None of the 20 patients had a relapse



F g 44 (t p) —Cy t av ty nd l w pow W ll n th a ns t t d s fib u t s

F g 45 (bottom) —Cy t ty d l w pow h wing ea f n pec fi bron inflamm t y t on n p t f w ll a d p rt l p h l t

(C rtesy f Tch rsk ff I G t l Sea V w H p Bull 14 347 169 July 1957)

Man 40 acquired tuberculosis in 1951 for which he was treated in several hospitals In 1953 sputum was positive and he had extensive fibrocaseous and cavernous tuberculosis involving the entire left lung The upper two thirds was destroyed by a giant cavity There was extensive bronchogenic spread from the hilus to the lower two thirds of the right side (Fig 43) He received streptomycin and isoniazid Sputum was alternately positive and negative until 5 months after operation

Pathologic examination showed marked pleural thickening and a cyst 12 14 cm in diameter occupying 75% of the upper lobe The wall was dense fibrous tissue (Fig 44) Sections of large bronchi

showed no evidence of active tuberculosis Fibrosis was seen in some with tubercles and occasional irregular caseous necrosis (Fig 45)

Fatal Hepatic Necrosis Associated with Aminosalicylic Acid Review of Literature and Report of Case are presented by David Paine[7] (Waltham Mass ) Five fatal hypersensitivity reactions to aminosalicylic acid (PAS) have previously been reported 3 with liver involvement

Fever without eosinophilia or rash may be the first symptom Arthralgia is also early By the time a rash has appeared and before jaundice is seen irreversible and fatal progressive hepatitis may be under way Unexplained fever in a patient taking PAS requires immediate withdrawal of the drug which should then be withheld until a hypersensitivity reaction can be excluded Test doses of PAS unless minute are dangerous

Woman 29 with proved tuberculosis was started on isoniazid 300 mg and PAS 10 Gm daily On the 17th day she had headache and generalized pain in the extremities On the 22d day she had back ache *was vomiting and had a fever of 102 F PAS was discontinued* and the fever began subsiding She was then given by error 3 3 Gm PAS That afternoon the temperature rose to 103 F and a morbilliform rash appeared on the face chest abdomen and thighs Liver function tests became abnormal and 3 days later she was clinically jaundiced The jaundice progressively worsened and she became stuporous and irrational and died 6 weeks after antituberculous therapy had been started

Autopsy revealed severe acute toxic necrosis of the liver bile necrosis petechial hemorrhages of the intestinal mucosa gastromalacia icterus passive congestion of the spleen and moderately advanced active pulmonary tuberculosis

► [The number of reported fatalities from PAS toxicity is undoubtedly far below their actual occurrence This case report illustrates dramatically the importance of the early recognition of hypersensitivity reactions to this widely used drug Paine points out the little known dangers of attempting desensitization and also cites instances of sensitization occurring simultaneously to more than one drug when such agents as PAS isoniazid and streptomycin are administered concurrently Such cross sensitization reactions are not uncommon and their possibility should be considered when the original choice of a drug regimen is made Thus in cases of tuberculosis in which isoniazid alone may be expected to do as well therapeutically as a two drug regimen as in noncavitary pulmonary tuberculosis for instance there is excellent reason to minimize the risk by using the single drug regimen —Ed ]

(7) J A M A 167 285 289 My 17 1958

Aspiration Biopsy of Parietal Pleura Results in 45 Cases are reported by Robert F Donohoe Sol Katz and Mary J Matthews[8] (Washington D C) Pleural effusion may be the primary feature of an illness in which all diagnostic tests cannot reveal the cause Inability to demonstrate tubercle bacilli from aspirated pleural fluid or from culture of gastric washings or sputums is not sufficient basis to eliminate tu berculosis as the cause In 65% of patients with pleural effu sion frank pulmonary and/or extrapulmonary tuberculosis can be expected within 5 years Aspiration biopsy of the parietal pleura may provide the diagnosis when other meth ods have failed

At the time of biopsy all 45 patients had x ray evidence of pleural effusion or residual pleuritis Some had more than one biopsy if the original specimen was inadequate In all but 1 biopsy was performed at the time of the first thora centesis If the tissue obtained was inadequate or the result was not compatible with the clinical impression or if non specific inflammation of the pleura was reported aspiration was repeated if fluid was still present or open surgical biopsy was done

Method—The equipment required is a Vim Silverman biopsy needle The fluid is located by fluoroscopy or x ray With use of local anesthesia the pleural space is entered and fluid withdrawn All the necessary specimens are obtained at this time to avoid later contami nation with blood from the biopsy site When fluid is obtained freely the needle is withdrawn to a point at which the flow suddenly ceases a Kelly clamp is attached to the needle at skin level and the syringe and needle with Kelly clamp attached are completely withdrawn The dis tance from the end of the needle to the clamp is measured and trans ferred to the biopsy needle which is inserted up to the level of the clamp This theoretically places the edge of the needle at the parietal pleura increasing the chances of obtaining parietal pleura and de creasing those of injuring visceral pleura and the underlying lung The obturator is withdrawn and the biopsy shaft is introduced and inserted until resistance is encountered The shaft is then advanced about 0 5 1 cm followed by advancement of the outer sleeve rotation of the biopsy shaft 360 degrees and withdrawal Until the obturator is replaced the orifice should be covered with the sterile gloved finger to prevent inflow of air

(8) Am J Med. 2 883 893 J 1957

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(8) Am J M 4 2 865 893 J 1957

Of 23 patients suspected clinically of having tuberculous pleuritis 12 were proved to have this by aspiration biopsy and 7 others shown to have nonspecific pleuritis or inadequate tissue by aspiration had granulomatous pleuritis at open biopsy making a total of 19 cases of pleuritis due to tuberculosis Two other patients showed nonspecific involvement at both aspiration and open biopsy 1 had a pancreatic cyst with nonspecific pleuritis and 1 refused repeat aspiration or open biopsy Among 11 patients considered to have malignant pleural effusions clinically adequate pleura was obtained in 8 and in 4 confirmed the presence of malignancy Three showed nonspecific pleuritis and 1 normal pleura but all 4 were proved to have malignancy by surgery or autopsy

Aspiration biopsy of the parietal pleura is safe easy and accurate in obtaining early diagnosis Histologic diagnosis of nonspecific pleuritis does not eliminate possibility of tuberculosis or malignancy as the etiology Open biopsy should next be performed if not contraindicated It is most useful in patients with tuberculosis suspected

**Tuberculous Pleural Effusions Treated by Antibacterial Therapy** Peter A Emerson[9] (London) treated 102 previously healthy patients Admission x rays showed no parenchymal lung lesion Effusion was confirmed in each case by aspiration of typical straw colored fluid Most patients were treated with combined streptomycin and PAS or streptomycin and isoniazid The dose of PAS was 12 20 Gm daily by mouth of isoniazid 200 300 mg daily and of streptomycin 1 Gm daily intramuscularly A fourth of the patients were treated by rest in bed for at least 3 months but the others were allowed to get up when fever and toxemia had subsided

No statistical difference was apparent in duration of fever between patients treated with bed rest and the others Antibacterial therapy had no effect on duration of elevated sedimentation rate pleural effusion or pyrexia Adequate follow up was available in 100 patients and 8 of these had further manifestations of tuberculosis This compares favorably with previously reported results in patients who received no antibacterial drugs and in whom incidence was 30% With adequate therapy morbidity was reduced to 1%

(9) Lancet 2 674 676 Oct 5 1957

**A 10 Years Study of Spontaneous Pneumothorax in a Community** Most accounts of pneumothorax have been based on statistics from large hospitals with selected patient loads N Wynn Williams[1] reviewed all cases of pneumo thorax that occurred during 10 years at the Bedford General Hospital (England) and its attached chest clinic The pop ulation covered was about 150 000 about one third in a county town and the rest in surrounding urban and rural communities Diagnosis was made by x ray in each case

A total of 74 pneumothoraxes was seen in 70 patients 59 of whom were men The left side was affected more often than the right The most frequent age at onset was between 20 and 39 though cases occurred in the 7th decade also In 52 onset was acute with sudden pain and/or rapidly increas ing shortness of breath This was most common in patients under age 40 The large pneumothoraxes were most com monly associated with acute onset

Treatment depended on degree of dyspnea initially If distressing air was removed Otherwise natural re expan sion was allowed and it occurred in 49 of the 74 pneumo thoraxes If re expansion was delayed more than 14 days air was removed In 7 patients treatment was considered urgent and 3 of these had pneumothoraxes under positive pressure All 7 had bronchopleural fistulas treated by insertion of a Foster Carter needle or intrapleural catheter attached to an underwater seal

Seven patients had more than 1 pneumothorax No deaths occurred in patients who had no other disease of the lungs or heart The possible etiology of the pneumothorax was known in 41 patients 6 had bronchiectasis 11 chronic bronchitis and emphysema 4 healed pulmonary tuberculosis and 2 sar coidosis bullae were noted in 4 and small apical linear shad ows suggesting apical emphysema in 9 Pneumothorax fol lowing pyogenic infection of the lung or adjacent structures was uncommon except as a complication of staphylococcic pneumonia in young children In only 1 patient did pul

(1) Th x 12 253 257 S pt mbe 1957

monary tuberculosis develop and this appeared only after 3 years

► [Another valuable community study by Wynn Williams whose outstanding report on *bronchiectasis in Bedford is recalled (1954-55 Year Book* p 151) —Ed ]

**Spontaneous Pneumothorax in Royal Navy** All cases are considered to be in this category when pneumothorax appears without demonstrable cause in healthy persons in whom tuberculosis is excluded and fever and pleural effusion are absent The condition can no longer be regarded as rare apparent increase in incidence is due to improved diagnosis J M Cliff' reviewed all admissions to 3 naval hospitals from 1943 to 1953 and found that 163 patients (3 women) had had spontaneous pneumothorax

The young adult male is particularly prone to spontaneous pneumothorax probably because emphysematous blebs are

NUMBER OF PATIENTS TRACED IN EACH YEAR

| Year | 1943 | 1944 | 1945 | 1946 | 1947 | 1948 | 1949 | 1950 | 1951 | 195 | 1953 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of cases in original investigation | 0 | 14 | — | 17 | 16 | 11 | 9 | 10 | 9 | 13 | 22 |
| No traced | 14 | 10 | 14 | 10 | 1 | 8 | 5 | 8 | 7 | 9 | 19 |
| Deaths | 1 | 1 | — | — | — | — | 1 | — | — | — | — |
| No with ut recurrence | 13 | 8 | 13 | 8 | 9 | 7 | 4 | 7 | 6 | 8 | 19 |

more likely to develop in the sex which plays more active sports performing feats which require intrapleural hypertension against a closed glottis Previous history of pulmonary disease is uncommon and only 11% had had a respiratory infection Of 100 patients in whom activity was recorded at time of onset of pneumothorax 36 were at rest or asleep and 48 were exercising mildly and 16 strenuously Only 1 patient was completely asymptomatic

Later recurrence is frequent often with no evident predisposing cau e Instructions to lead quiet lives to avoid closing the glottis and to avoid high altitudes or heavy lifting seem unnecessary because relapses apparently occur while the patient is either resting or active Follow up was available in 119 patients (table) An ipsi contra or bilateral pneumothorax recurred in 12% Three fourths of the patients traced were asymptomatic the others attributed breathlessness on exertion or winter bronchitis to the spontaneous pneumothorax There was no relation between previous spontaneous pneumothorax and subsequent pulmonary tuberculosis If it is truly a spontaneous pneumothorax it is

( ) P oc Royal Soc M d 50 517 526 J ly 1957

a benign condition and a person so affected is no more likely to acquire pulmonary tuberculosis than the average person Tuberculosis must be excluded as the cause of the pneumothorax when it first occurs

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## DISEASES OF THE DIAPHRAGM

**Traumatic Rupture of Diaphragm Clinical Manifestations and Surgical Treatment** Many types of trauma may cause diaphragmatic rupture including gunshot stab wounds and blunt injuries and subphrenic septic processes The most common cause is now impact injury in automobile crashes Gerard Desforges John W Strieder Joseph P Lynch and Irving M Madoff[3] (Boston) report experience in 16 cases Nine patients were drivers or passengers in motor vehicles 4 were struck by a motor vehicle and 3 had fallen Only 1 had no associated serious skeletal injury

The most prominent symptom was shortness of breath present in 11 of the 16 Cardiopulmonary insufficiency was most striking in the early posttraumatic period Two patients were asymptomatic and diagnosis was suggested by plain films taken for other purposes Three had gastrointestinal symptoms 2 of the 3 had vomiting and 1 of these 2 had left shoulder pain precipitated by heavy meals in the third acute large bowel obstruction developed

The most important diagnostic aids are history and serial plain x rays of the chest These alone led to correct diagnosis in 13 of the 16 patients Chest films taken with a Levin tube in the stomach were required in 1 and barium studies in the other 2

X ray examination is the single most valuable tool in confirming the suspicion of diaphragmatic rupture In the posteroanterior view obliteration of the diaphragmatic angle deformity of the diaphragmatic contour atelectasis of the lower lobe and pneumothorax in the lower chest—all suggest diagnosis of ruptured diaphragm Repeat films after introduction of a nasogastric tube may often show the intrathoracic portion of the stomach Barium studies showing the stomach and colon in the thorax serve the same purpose

(3) J Th  ic Su g 34 779 799 December 1957

Occasionally barium will not pass into the intrathoracic portion of the stomach because of obstruction at the site of the tear and secondary torsion of the stomach If the right diaphragm is involved these technics will not necessarily be helpful but a barium enema may show an elevated hepatic flexure

In the acute phase the patient may be seriously injured and the diaphragmatic injury may be masked by other serious concomitant trauma In the chronic phase diagnosis may be confused with vague upper abdominal chronic gastrointestinal disease In the intermediate phase there are symptoms of acute high or low intestinal obstruction and emergency surgery may be necessary

**Esophageal Hiatus Hernia of Diaphragm Analysis of Surgical Results** George H Humphreys II Jose M Ferrer Jr and Philip D Wiedel[4] (*Presbyterian Hosp New York*) present the long term follow up in 97 operations The esophageal hiatus of the diaphragm is formed by the right crus which normally surrounds the esophagus just above the cardia to form an oval slinglike aperture The pinchcock action of the hiatus depends on its slinglike configuration and contributes to the prevention of reflux from stomach to esophagus (Fig 46)

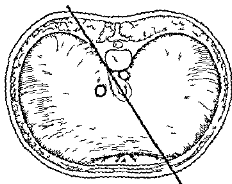
The phrenoesophageal ligament an upward extension through the hiatus of fibers from the infradiaphragmatic layer of the transversalis fascia invests the cardia and lower most esophagus in a sheath and inserts into the adventitia of the esophagus When well developed this ligament is a major factor in holding the cardia below the diaphragm A second anchor is the left gastric artery and its mesentery which tethers the cardiac portion of the lesser gastric curve to the posterior abdominal wall

Reflux through the cardia is normally controlled by intrinsic mechanisms in the so called cardiac sphincter muscle aided by a sling of gastric musculature which surrounds the esophagogastric junction The terminal esophagus or epiphrenic ampulla also helps prevent reflux The mechanisms are effective only it the normal acute esophagogastric angle at the cardia is preserved

There are three main types of acquired hiatus hernia Most common is the sliding hernia In this the cardia lies

(4) J Thorac S g 34 749 767 De mbe 1957

a variable distance above the diaphragm and the cardiac end of the stomach slides up retroperitoneally and retro pleurally A true peritoneal sac is not present but a fold of peritoneum may be pulled up by the sliding stomach In large sliding hernias this sac may be large enough to allow gastrocolic omentum or even colon to pass into the chest The hiatus is dilated the phrenoesophageal ligament stretched and thinned and the left gastric vessels long and lax The esophagogastric angle is obtuse the valve is no



F g 46—D ph gm f om bo h w g m cula l g f soph g l h tus m d f m ght u Obl q ( p t d cated h h y l n (C y of Humph ey G H H t l J Th Su g 34 749 767 D mb 1957)

longer present and the cardiac sphincter alone cannot pre vent gastric reflux with its resultant symptomatic esopha gitis The esophagus is short either because the longitudinal muscle is contracted or because of scarred fibrous contraction secondary to inflammation The former is more frequent and the esophagus readily resumes its normal length when the cardia is replaced below the diaphragm If the latter is the cause esophageal length is less easily regained and repair is less satisfactory (Fig 47)

A special subtype of sliding hernia is the esophagoaortic hernia protruding through a common hiatus between the esophagus anteriorly and the aorta posteriorly This type was seen in 2% of the patients A paraesophageal hiatus hernia in which the phrenoesophageal ligament and the left gastric vessels are firm and hold the cardia and lesser curva ture below the hiatus was present in 6% The fundus and greater curvature of the stomach protrude up beside the

cardia and esophagus into a peritoneal sac in the mediastinum In the combined type seen in 3% the cardia is above the diaphragm though the fundus and greater curvature are rotated upward to an even higher position so that a sac

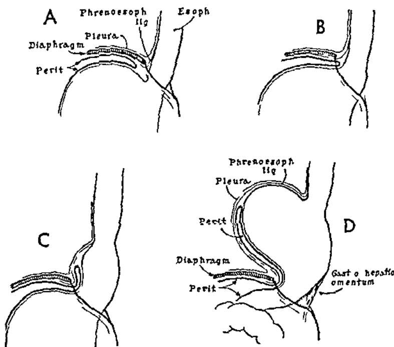



*Fig 47*—H t s n pl e d c ted F gu e 46 *A* no mal H t s l es alm t ert c lly w th esoph gu p ng bl quely f rwa d into toma h. Per to m effected onto d ph agm nte o t card a No pe t eum po t n r to es dia. *B* fir t stage of sl d ng h rnia C rd s abov hiat nd esophagu has lost its acute a gle of entra c nto st ma h H tus s enl rg d by preading of poste i r u al fiber Anterior per toneal f ld h s bee d awn backwa d and j t at hiatu b t i not act ally n tho ax *C* e o d stage E oph gus h s hortened and ca d well abo e diaph agm H tu ha nia g d ante ly and poste orly a d f ld of pe toneum has ente d ch t rolling back f om stomach as latt rises *D,* dvanced stage. Gastrohepat c ve sels though st et hed, t nd t hold po t romedial, lesse r curvature aspect, but f ether a te o h at t etch g ha llowed f ndus to roll upwa d to pos tion high th n ca d car y ng la ge fold f perito eal a w th it. Ultimat ly gast ocolic ome tum o colon may pa s upwa d t th s sac (C urte y of Humph eys G H II, *et l* J Tho c Su g *34* 749 767 Decembe 1957)

containing other abdominal viscera may be present True congenital short esophagus hiatus hernia is rare It was found in only 1 patient

The characteristic symptoms of a sliding hiatus hernia are secondary to reflux of stomach contents heartburn substernal and epigastric pain a pulling sensation in the throat

and episodes of sudden choking especially when the patient is recumbent at night If esophagitis is present dysphagia may be extreme or the patient may have hematemesis Extreme aerophagia and belching are frequent Symptoms are often confused with cholecystitis and angina In paraesophageal hernia dysphagia and digestive symptoms are less frequent because the cardia is competent When symptoms are present they are often due to pressure on the heart or lungs The hernias occasionally become incarcerated True congenital hernias may cause intractable vomiting in infants in adults symptoms are similar to those of the sliding hernias

Prognosis after surgery depends on type of hernia and of surgery In sliding hernias results of transthoracic surgery were good in 42 83% Transabdominal operations in 8 patients produced good results in only 2 Paraesophageal and esophagoaortic hernias require more complex operations *often for acute incarceration In only a few are fair to good* results obtained Surgery is effective in alleviating symptoms in a high proportion of uncomplicated cases of sliding hernia Early operation is indicated ✓

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## MISCELLANEOUS

**Chronic Disseminated Histiocytosis X (Schuller Christian Disease) with Pulmonary Involvement and Impairment of Alveolar Capillary Diffusion** Eosinophilic granuloma of bone Letterer Siwe disease and Schuller Christian disease are apparently different expressions of the same distinctive histiocytosis of unknown etiology and the clinical differences result from differences in localization the number and extent of the lesions and their different rates of progress Attilio D Renzetti Jr Gerard Eastman and J Howland Auchincloss Jr[5] (State Univ of New York Syracuse) describe a patient who had chronic disseminated histiocytosis X with pulmonary involvement documented by x rays from the onset Pulmonary function studies were carried out before and during therapy with adrenocortical steroids

Man 32 was dyspneic for 1 year At age 20 a chest film was nor

(5) Am J Med 22 834 840 M y 1957

mal but at 23 he had diffuse bilateral finely nodular and linear infiltration An osteolytic lesion of the right ilium and left femur and a biopsy specimen of a right supraclavicular lymph node revealed non lipid histiocytosis Symptoms of polydipsia and polyuria were diagnosed as diabetes insipidus and were controlled by Pitressin® Two years later osteolytic lesions were seen in the skull At age 31 dyspnea and cyanosis became severe Fine rales were heard over the entire right lung He had gallop rhythm hepatomegaly and clubbing of the digits Serum carbon dioxide was 40 vol % A chest x ray showed more extensive and coalescent infiltrations Pulmonary function studies showed reduction in the oxygen diffusing capacity of the lung marked hypoxia and hypercapnia After treatment with prednisone lung volume maximum ventilatory capacity and arterial blood gas content increased The patient became worse clinically and died

Autopsy revealed bilateral pleural fibrous adhesions marked diffuse interstitial fibrosis and focal chronic interstitial pneumonitis There were multiple recent and organizing pulmonary emboli and hemorrhagic infarcts The right ventricle was dilated There were healed nondeforming mitral valvulitis and aortic valvulitis with early aortic stenosis Focal histiocytosis was found in the vertebral bone marrow consistent with disseminated chronic histiocytosis

The diffusing capacity of the lung for oxygen and carbon dioxide was probably not changed by treatment The benefit must be attributed to improvement of alveolar ventilation perfusion relations reflected in the reduction of the percentages of dead space and venous admixture Similar responses to steroids have been reported in other types of alveolar capillary blocks Disseminated histiocytosis X should be considered in the differential diagnosis of diffuse pulmonary disease of unknown etiology Scalene node biopsy and an x ray survey of the entire skeleton should be done in such cases

**Idiopathic Pulmonary Hemosiderosis Report of Case with Apparent Remission from Cortisone** This is a rare disease of children and young adults with a well defined clinical course of hypochromic anemia intermittent pulmonary bleeding progressive pulmonary fibrosis and eventual terminal cardiorespiratory failure The cause is unknown John M Irvin and Paul W Snowden[6] (Monroe Wis) treated 1 patient with cortisone

Boy 16 had fatigue pallor lack of energy and shortness of breath He had anemia He was treated with rest and iron gradually gained weight and the anemia improved Symptoms recurred next year and hospitalization was again required 2 months after iron was stopped At this time he had splenomegaly and a chest x ray showed diffuse finely mottled densities throughout the entire lung fields He subse

(6) A M A J D Child 93 182 187 Feb u y 1957

quently had episodes of hemoptysis chest tightness low grade fever and fatigue Many hemosiderin laden macrophages were present in sputum and fasting gastric aspirate (Fig 48) Cortisone was given then dosage was gradually reduced and finally it was discontinued. The patient has been asymptomatic for 9 months Vital capacity is normal and the chest x ray is clear except for a diffuse fin ly gran ular infiltration.

The most significant laboratory test for the disease is the finding of hemosiderin laden macrophages in the sputum



F g 48—M ph g put m l d w th d p t l st d h m d g l Pru bl act d d f m ×600 (C rt y f Irv J M d S wd P W A M A J D Ch ld 93 182 187 F bru y 1957)

or in the fasting gastric aspirate Hemosiderin appears as clumps of yellow brown granules in the cytoplasm of the macrophages The granules stain deep blue with the Prus sian blue reaction of potassium ferrocyanide and hydro chloric acid Aspiration needle biopsy of the lung has proved valuable when sputum or gastric contents are unavailable

**Respiratory Complications of Influenza** The recent epi demic of Asian influenza has in general been mild but many patients required hospitalization for complications W C Walker A C Douglas W J H Leckie A Pines and I W B

Grant[7] (Edinburgh) summarize the findings in 125 patients admitted during a 6 week period in 1957 The diagnosis was *clinical confirmed in the 12 who were so studied by positive* serologic evidence By clinical criteria the diagnoses were divided into laryngotracheitis bronchitis or bronchiolitis by x ray evidence of pulmonary consolidation into segmental lobar and lobular lesions (Table 1)

Those with laryngotracheitis presented with hoarseness retrosternal pain and an irritating cough usually dry but occasionally productive of scanty tenacious sputum Some had evidence of respiratory obstruction in that after paroxysms of coughing they became intensely breathless and

TABLE I —CLINICAL RADIOGRAPHIC CLASSIFICATION SHOWING NUMBERS IN EACH GROUP

| Type of case | Without chronic respir tory di se | W th chron c resp ratory di ease | Tot l |
|---|---|---|---|
| *Lary g tr he* | 10 | 4 | 14 |
| *B h t b o h ol* | 7 | 35 | 42 |
| *Pn m* | | | |
| Lob egmental | 17 | 11 | 28 }69 |
| Lobul | 18 | 23 | 41 } |
| | 52 | 73 | 125 |

deeply cyanosed One of these 14 later developed staphylococcic lobular pneumonia and another mild segmental pneumonia the others recovered in a few days

In the patients with chronic bronchitis the episode of influenza was indistinguishable from a typical infective exacerbation Dyspnea cyanosis and prostration were prominent Staphylococcus pyogenes were isolated from 3

Of the 69 who had pneumonia 33 were over age 60 and 2 under 20 The pyrexia was somewhat longer but otherwise the clinical picture did not differ from usual cases of pneumonia The most striking single feature was the extent of the lesions massive bilateral consolidation being fairly common and the rapidity of onset and degree of toxemia The 6 with fulminating staphylococcic lobular pneumonia had initial symptoms of influenza rapidly followed by hoarseness retrosternal pain cough intense dyspnea central cyanosis and profound prostration

In 40% of the 125 patients an antibiotic most commonly penicillin had been given for 1-4 days before admission to

(7) Lancet 1 449-454 Ma 1 1958

hospital In 68 patients no specific organism was isolated Of the 31 in whom the predominant organism was Staphylococcus pyogenes 22 had pneumonia (lobar or segmental in 9 lobular in 13) It was isolated in all 6 fulminating cases and from 9 of the 15 patients who died The sensitivities (Table 2) showed only 45% sensitive to penicillin Superinfection with staphylococci was believed to have occurred in 12

Combined penicillin streptomycin and chloramphenicol was used in 33 patients most of whom were treated during the early part of the epidemic 51 received penicillin plus streptomycin 17 penicillin alone 6 erythromycin plus penicillin 6 penicillin and chloramphenicol 4 chloramphenicol

TABLE 2—Sensitivities of Staph pyogenes Isolated on Admission in 31 Cases*

| Antibiotic | Sensitivity | | | | | |
|---|---|---|---|---|---|---|
| Penicillin | S | R | S | R | R | R |
| Streptomycin | S | S | R | S | R | R |
| Chloramphenicol | S | S | S | S | S | R |
| Tetracycline | S | S | S | R | R | R |
| Erythromycin | S | S | S | S | S | S |
| Total | 14 | 11 | 1 | 1 | 3 | 1 |

* S = sensitive; R = resistant

alone and 8 tetracycline alone Twelve received corticosteroids 4 because of previous long term therapy and 8 with fulminating pneumonia purely on an empirical basis No dramatic benefit was noted in the latter Oxygen therapy was needed by 36 Steam tents relieved retrosternal pain in some but did not relieve obstructive symptoms in the 6 treated for these Tracheostomy was lifesaving in 2 Most patients cleared their bronchial secretions by coughing in doubtful cases coughing was regularly supervised and when cough was ineffective secretions were aspirated through a bronchoscope Repeated accumulations of secretions were an indication for tracheostomy in 3

All 14 patients who had laryngotracheitis recovered uneventfully in a few days Of the 42 with bronchitis and bronchiolitis 39 recovered completely and 3 died 1 who had acute exacerbation of chronic bronchitis died of congestive cardiac failure and 2 died with bronchiolitis 1 of whom had Hamman Rich fibrosis the other chronic asthmatic bronchitis Of the 69 with pneumonia 50 recovered completely

Grant[7] (Edinburgh) summarize the findings in 125 patients admitted during a 6 week period in 1957 The diagnosis was clinical confirmed in the 12 who were so studied by positive serologic evidence By clinical criteria the diagnoses were divided into laryngotracheitis bronchitis or bronchiolitis by x ray evidence of pulmonary consolidation into segmental lobar and lobular lesions (Table 1)

Those with laryngotracheitis presented with hoarseness retrosternal pain and an irritating cough usually dry but occasionally productive of scanty tenacious sputum Some had evidence of respiratory obstruction, in that after paroxysms of coughing they became intensely breathless and

TABLE 1—CLINICAL RADIOGRAPHIC CLASSIFICATION SHOWING NUMBERS IN EACH GROUP

| Type of case | Without chronic respiratory disease | With chronic respiratory disease | Total |
|---|---|---|---|
| *Laryngotracheitis* | 10 | 4 | 14 |
| *Bronchitis or bronchiolitis* | 7 | 35 | 42 |
| *Pneumonia* | | | |
| Lobar segmental | 17 | 11 | 8 }69 |
| Lobular | 18 | 23 | 41 } |
| | 52 | 73 | 125 |

deeply cyanosed One of these 14 later developed staphylococcic lobular pneumonia and another mild segmental pneumonia the others recovered in a few days

In the patients with chronic bronchitis the episode of influenza was indistinguishable from a typical infective exacerbation Dyspnea cyanosis and prostration were prominent Staphylococcus pyogenes were isolated from 3

Of the 69 who had pneumonia 33 were over age 60 and 2 under 20 The pyrexia was somewhat longer but otherwise the clinical picture did not differ from usual cases of pneumonia The most striking single feature was the extent of the lesions massive bilateral consolidation being fairly common and the rapidity of onset and degree of toxemia The 6 with fulminating staphylococcic lobular pneumonia had initial symptoms of influenza rapidly followed by hoarseness retrosternal pain cough intense dyspnea central cyanosis and profound prostration

In 40% of the 125 patients an antibiotic most commonly penicillin had been given for 1-4 days before admission to

(7) Lancet 1 449-454 Ma 1 1958

both in the bowel and the tracheobronchial tree and pancreas

Woman 60 had a radical right mastectomy for adenocarcinoma Six years later she had chills fever and purulent blood tinged sputum treated with penicillin but after the 3d injection massive purpuric swelling of both lower extremities developed X rays showed right midlung infiltration and left pleural effusion negative for tubercle bacilli or tumor cells Cough persisted productive of small amounts of tenacious blood streaked sputum and the patient had fever loose




F g 49 —T ach and ght b h h w g p d memb xud t (Cou t y f S l mon F A J d F en y W J A I t M d 47 161 171 J ly 1957 )

bowel movements smoky urine anorexia fatigue weight loss and hematemesis On admission 5 months later she had anemia a normal white blood cell count 4 plus albuminuria and hemolytic Staph aureus was cultured from the urine She was treated successively with chlor tetracycline tetracycline and erythromycin Four days before death a blood specimen was cultured which 2 weeks later yielded Staph aure us The day before death she had multiple liquid green brown stools Escherichia coli and Bacillus proteus were cultured from these

At autopsy the trachea and larger bronchial surfaces appeared thick and rough from a fibrinous exudate forming a crusty diphtherit ic type of exudate (Fig 49) Microscopically this was an extensive

7 had residual opacity thought to be pulmonary fibrosis and 12 died 5 had postpneumonia serous effusion

In patients with fulminating staphylococcic infection the prognosis is probably related more to the virulence of the infection than to treatment However unrelieved respiratory obstruction is an important cause of death and requires emergency treatment Chemotherapy must be started with the assumption that the causal organism may be resistant to one or more of the commoner antibiotics

Antibiotic therapy should be restricted at the earliest possible stage to the effective minimum thus decreasing the opportunities for cross infection All patients with a tracheostomy should be isolated and strict barrier nursing technic enforced Patients with sputum should have cultures weekly and should be isolated if resistant staphylococci are grown All patients and staff should have nasal swabs weekly if they harbor coagulase positive staphylococci they should be treated with ointment of chlorhexidine or neomycin and bacitracin Patients with pneumonia should be treated with penicillin and streptomycin until bacteriologic studies indicate a specific drug

► [It is of particular interest that staphylococcic infection was regularly found in the patients with fulminating pneumonia Few similarly comprehensive reports are yet available from American clinics The experience here in the recent influenza epidemic follows much the same pattern however except that in a proportion of the fulminating cases no bacterial infection was established and death resulted apparently from an uncomplicated viral pneumonia —Ed ]

**Pseudomembranous Tracheobronchitis Pancreatitis and Enterocolitis Report of Case Complicating Antibiotic Therapy of Pneumonia and Septicemia** is presented by Frank A Solomon Jr and William J Feeney[8] (St Mary s Hosp San Francisco) Pseudomembranous enterocolitis is well recognized as a complication of antibiotic therapy apparently caused by overgrowth of bacteria resistant to the antibiotic used for the primary infection Micrococcus pyogenes (Staphylococcus aureus) is most consistently involved The incidence of this complication apparently is correlated with the increased use of antibiotic drugs Pseudomembrane formation in respiratory passages was reported in 1926 and hemolytic Staph aureus hemolytic streptococcus and Staph albus have been isolated fom patients so affected This case is the first in which pseudomembranous changes occurred

(8) Ann I t Med 47 161 171 July 1957

the infection Serologic studies are most important in establishing diagnosis Chloramphenicol is the antibiotic of choice for therapy

Long Standing Intrabronchial Foreign Bodies present problems different from those recently inhaled The original incident may be unremembered the presence of superimposed atelectasis pneumonitis bronchiectasis or lung abscess confuses the clinical picture and the bronchoscopic appearance is often misleading J S A Linton[1] (London) presents 16 cases Only 5 patients volunteered a history of inhaling a foreign body and 5 recalled the incident only after the foreign body had been removed In 6 no relevant history was obtained even in retrospect The interval between inhalation and removal varied from 6 months to 9 years Of the 16 patients 14 were adults

Presenting symptoms were cough and constant purulent sputum with frequent febrile incidents In several symptoms appeared some time after the original obstruction readily relieved by symptomatic treatment with antibiotics and physiotherapy but recurring at intervals until the foreign body was removed Hemoptysis in 9 cases was severe in 3 The right side was affected more often than the left the lower lobe more commonly than the upper

Routine chest films revealed those foreign bodies which were metal In the others x rays showed atelectasis pneumonitis or abscess with no indication of the cause Bronchography was of no help Bronchoscopy was conclusive when the findings were correctly interpreted Even if the foreign body was not seen friable granulation tissue was heaped up surrounding and obscuring it Biopsy showed normal mucosa granulation tissue or squamous metaplasia

The choice of treatment is difficult even after diagnosis is established In 3 cases carcinoma was incorrectly diagnosed with resection the correct diagnosis was made only at pathologic examination The case diagnosed as lung abscess was also treated by resection One patient thought to have residual bronchiectasis coughed up a foreign body after 6 years and was thereafter asymptomatic Of the 11 correctly diagnosed foreign bodies 1 was coughed up 5 extracted at bronchoscopy 1 removed by bronchotomy and 4 resected All patients treated without resection had complete relief from

(1) Th ax 12 164 170 J 1957

necrotizing process destroying the entire mucosa over large areas Where it was most intense there was fibrinoid necrosis In some areas fibrous reaction indicated the process had persisted several weeks or more possibly many months Similar necrotic areas were present in the small bowel The pancreatic ducts showed areas of ulceration and infiltration with polymorphonuclear cells Postmortem culture from the lungs grew hemolytic and nonhemolytic Staph aureus

► [As the authors point out there has been no parallel increase of case reports of psuedomembranous staphylococcal infection in the respiratory tract during the past five year period in which pseudomembranous enterocolitis has been reported with increased frequency These infections as well as drug resistant staphylococcal infections generally are widely regarded as complications of antibiotic therapy The higher incidence of drug resistant staphylococcal infections acquired inside than outside hospitals suggests however that the problem is perhaps more one of housekeeping procedures and aseptic technics than of the overuse of antibiotics Indeed where this aspect of the problem has been recognized and the procedures improved the incidence of drug resistant staphylococcal infections has been sharply reduced —Ed ]

**Salmonella Pleuropulmonary Disease** Four cases are reported by William Weiss George M Eisenberg and Harrison F Flippin[9] (Philadelphia) All were in men 2 of whom were in the 8th decade All had some fever but only the 1 patient who had acute onset with gastroenteritis showed leukocytosis The pleuropulmonary disease was suppurative in 3 as empyema in 1 and lung abscess in 2 and the 4th patient had a terminal pneumonitis without evident suppuration in the course of disseminated carcinoma All 4 patients had complications involving the genitourinary tract with infection in 3 and carcinoma in 1

The species of Salmonella isolated were typhimurium in 2 newport in 1 and new brunswick in 1 All organisms were isolated from the respiratory tract including the sputum in the 3 who had involvement of the pulmonary parenchyma In 1 patient the same organism was isolated from the blood, stool and urine this was the patient who had septicemia He was one of the 2 who had received prior cortisone therapy

All patients were treated with broad spectrum antibiotics Three recovered The patient with terminal carcinoma died All but 1 received chloramphenicol with or without other broad spectrum agents Surgical drainage was instituted in the patient with lung abscess and in the 1 with empyema

Salmonella infection of the respiratory tract is uncommon and is not necessarily accompanied or preceded by enteritis Cortisone therapy may be responsible for dissemination of

(9) Am J M Sc 233 487-496 M y 1957

of underlying carcinoma was considered and thoracotomy was recommended by the consulting surgeons and radiologists in each case Only the 2 earliest patients were subjected to thoracotomy and both proved to have unresolved pneumonia Two other patients died of intervening myocardial infarctions and at autopsy proved to have unresolved pneumonia The other 19 patients had no surgery Follow up examinations revealed slow resolution

The alcoholism absence of unusual respiratory symptoms before the acute illness sudden onset of widespread bacterial



Fg 50 (l ft) —Adm n x y f p t t w th ght pp l b p m
Fg 51 ( ght) —X y f m p t t tak pp x m t ly 7 w k l t
(C rt y f K by W M M t l N w E gl d J M d 2 6 8 8833 M y 2 1957 )

pneumonia involving at least 2 segments of the right upper lobe and negative bronchoscopy and sputum cytology serve to differentiate the syndrome of slowly resolving bacterial pneumonia from bronchogenic carcinoma

► [One wonders about a possible relationship of these cases to mucoid impaction of the bronchi (see Greer 1957 58 YEAR BOOK p 144 and Shaw *et al* Am Rev Tuberc 76 970 1957) Mucoid impactions occurs most frequently in patients with an asthmatic history however whereas the predisposing fact in these cases appears to have been chronic alcoholism Another point of difference is the lesser frequency in the cases of mucoid impaction of an acute pneumonic onset Nevertheless it is difficult to explain the rapid contraction of the lobe without some element of bronchial obstruction as a factor

This interesting report emphasizes that not all delayed resolution of pneumon a is caused by the presence of carcinoma and that with careful clinical study differentiat on may be possible —Ed ]

symptoms and resolution of physical and radiologic signs though the average history had been 3 years

Even with obvious infection and apparently complete obstruction lung damage may not be permanent and irreversible Simple removal of the foreign body by bronchoscopy or bronchotomy should suffice in many cases Neither the length of history nor profuse purulent sputum is an absolute contraindication to an attempt to preserve lung tissue Only in true abscess or gross bronchiectasis with fibrosis and parenchymal destruction is resection necessary

**Differentiation of Right Upper Lobe Pneumonia from Bronchogenic Carcinoma** Slowly resolving pneumonias may indicate the presence of underlying pulmonary neoplasms Even if sputum cytology bronchoscopy and special studies reveal no abnormalities thoracotomy is often performed because of the possibility of an underlying tumor However the risks of the thoracotomy are not negligible especially in elderly patients William M M Kirby Wayne S Waddington and Byron F Francis[2] (Univ of Washington) studied 23 patients in whom delayed resolution and partial collapse of the right upper lobe followed bacterial pneumonia Certain features allowed differentiation of these patients and forestalled surgery Follow up proved that tumor was not present

Of the 23 patients 21 were men and 22 had chronic alcoholism All were heavy smokers and all were over age 30 In each the illness began suddenly and two or more of the other manifestations of acute bacterial pneumonia—fever chills pleuritic chest pain and rusty sputum—were present In 9 pneumococci were grown from blood cultures In each 3 sputum specimens were negative for tuberculosis Sixteen had a leukocytosis In all chest x rays on admission showed extensive pulmonary consolidation involving at least 2 and in some 3 segments of the right upper lobe (Fig 50)

Antibiotics produced a prompt subjective response but the temperature was elevated for 10 21 days Instead of the usual prompt progressive clearing of pulmonary infiltrations these 23 patients showed a characteristic picture of partial collapse and delayed resolution in the right upper lobe (Fig 51) Sputum cytology and bronchoscopy were done in each case and in some scalene node biopsies The possibility

(2) New E gl d J M d 256 8 8833 M y 2 1957

# THE BLOOD *and* BLOOD-FORMING ORGANS

WILLIAM B CASTLE MD

# PART III

# THE BLOOD AND BLOOD FORMING ORGANS

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## GENERAL TECHNICS AND TOPICS

**Importance and Interpretation of Routine Blood Counts** Matthew Block[1] (Denver) condemns the complete blood count as a routine measure in all patients It is a gross waste of the patient s money and the laboratory s time The physician must differentiate between those procedures needed as screening tests for the average hospital admission and those needed for the differential diagnosis of a problem case

The red count has no place in screening procedures and should be used only in intensive studies of the type of anemia present in a diagnostic problem Hemoglobin and hematocrit are almost equally accurate and hemoglobin determinations are about a third as expensive

The white count has become a standardized procedure but the count can be closely approximated by careful inspection of the thin end of a peripheral blood smear studied under a magnification of about 100 It can be determined whether the white count is low normal elevated or grossly elevated and in a routine admission this is all that is necessary

Platelet counts even in the most practiced hands are unreliable Studying of the thin end or trailers of a peripheral blood smear can replace the count If easily seen under low power (100×) platelets are abnormally large and the count is too high If barely seen with this magnification they are normal If found with difficulty or not at all and if extremely small and hard to recognize they are decreased to absent [and clot retraction will be poor—Ed ]

Differential counts can be quickly estimated by scanning peripheral smears under low power This also allows evaluation of the cells The average technician performing a differential count is so engrossed in counting he does not see the

(1) Rocky Mou ta n M J 54 894-897 Septembe 1957

pressure with the thumb The blades are then held firmly in position as the needle cannula is passed over the greater part of their length by clockwise counterclockwise rotary motion As the retained biopsy specimen is always thicker distally than proximally the cannula cannot pass over the entire specimen The cannula and biopsy blades are firmly grasped in the fingers and palm and removed together A sterile gauze pad is placed over the puncture site and the patient applies pressure over the gauze

Wright s stain smears can be made from the material remaining within the biopsy blades after the specimen is removed Fixation in Zenker s solution for 24 hours decalcifies the minute bony spicules and the specimen can then be handled and sectioned by routine histologic methods and finally stained even with Wright s stain

Failure to obtain marrow by aspiration is usually significant [of hypoplasia sticky cells or myelofibrosis—Ed ] and further efforts to obtain bone marrow for study are imperative Surgical trephine introduces the complications of bone dust and requires at least a minor operating room and a surgical consultation and diagnosis is further delayed by the need of prolonged decalcification if cortical bone is included The Vim Silverman technic is so simple that it can be carried out without previous preparation when aspiration has failed and there is usually less discomfort than from aspiration

**Explanation of Discrepancy between Direct and Indirect Platelet Counts** In the direct method blood is accurately diluted with an anticoagulant usually in a hemocytometer pipet and the platelets are enumerated in a counting chamber For the indirect method blood is diluted and placed on an ordinary microscope slide spread and dried and the ratio of platelets to red cells is determined The red cells are then counted directly in a counting chamber and the platelet concentration is derived from the ratio A normal count by the direct method is about 250 000/cu mm by the indirect method 500 000/ cu mm This discrepancy has been known since the beginning of the century Harry J Fitch[3] (Walter Reed Army Med Center) demonstrates the reason for the difference

In the indirect method when the drop of fluid spreads beneath the cover slip especially if the drop is small and the cover slip is thin enough to be flexible the red cells concen

(3) Blood 12 671 676 J ly 1957

cells This is the direct result of undue emphasis on the magic of numbers

The reticulocyte count is important in the differential diagnosis of obscure anemias It is frequently a valid but indirect indication of hemolysis Any patient needing a red count probably should have a reticulocyte count The observant physician may save the expense of a reticulocyte count by estimating the number of diffusely basophilic red cells in the differential smear

Screening tests are sufficient for 90% of all hospital admissions and should include a hemoglobin or possibly a micro hematocrit determination a white count and differential smear If a hematologic problem exists a specimen should be obtained for hemoglobin red count hematocrit and bilirubin determinations and a smear carefully made for study of white cells platelets red cells and reticulocytes This basic information is necessary before any treatment If possible treatment should be delayed until diagnostic studies which should include bone marrow aspiration have been completed

► [A timely exhortation to be read in the original Lacking is only the additional emphasis that reticulocyte counts are useful indexes of acute changes in erythropoietic function induced by therapy or disease However as a Boston cover slip blood man I would no more use slides for making blood films than I would put tomatoes in clam chowder and for the same reason—they spoil the brew —Ed ]

Biopsy of Bone Marrow with Vim Silverman Needle William McFarland and William Dameshek[2] (Boston) find that in most cases simple aspiration provides sufficient marrow particles to study relative morphology and maturation but in about 6% the yield is inadequate In 20 consecutive cases in which aspiration failed they obtained diagnostic specimens by Vim Silverman biopsy

METHOD —The patient is placed in the lateral recumbent position with knees drawn up back flexed as if for lumbar puncture and the back at the edge of the table The posterior iliac crest and then the posterior superior iliac spine are located The skin is prepared and local anesthesia infiltrated A 2⅜ in Vim Silverman needle is introduced through the skin with gentle pressure and clockwise counter clockwise rotary motion penetrating the crest just cephalad to the posterior superior spine

With the point of the needle and obturator just inside the cortex of the bone the obturator is removed and the biopsy blades are inserted the length of the needle The blades are pushed the remainder of their length as in needle biopsy of the liver by firm steady forward

(2) J A M A 166 1464 1466 Mar 22 1958

differ Secretion tests on saliva show that the $A_1$ series belongs genetically to the male twin and the O series to the female

Mixed blood in dizygotic twins is common in cattle but rare in man Thus anastomoses between dizygotic human twins either must be rare or must develop after ancestral blood cells can no longer engraft in a foreign bed In monozygotic twins mixed blood must be common but not demonstrable Anastomosis between the chorion blood vessels of dissimilar bovine twin embryos was first demonstrated in 1916 and in 1945 the red cells of dizygotic twin cattle were shown to be antigenically a mixture of two kinds In 1953 the first human example was described and similar findings were reported for the first time in a pair of sheep twins in which the female proved to be a freemartin Probably all twin chicks are chimeras

Here the proportion of the two kinds of blood in one twin is independent of the proportion in the other In cattle each of the pair usually has the same mixture Both twins secrete the *ABH* antigens for which they have inherited genes but do not secrete antigens of their grafted red cells As with monozygotic twins skin might be successfully grafted from one twin to the other The first human chimera recognized a woman whose twin brother had died in infancy (1954 55 YEAR BOOK p 215) subsequently had children This indicates that the hormones of a human male fetus had no power to upset the normal sexual development of his female twin In the parallel situation a cow is sterile

**Hemoglobin M** This mathemoglobin with a unique spectrum absorption curve was first described in 1948 by Horlein and Weber in a family in which 4 generations were cyanotic The abnormality was found in the globin fraction A family of German extraction with a similar cyanotic condition affecting both males and females in at least 4 generations was discovered by Park S Gerald Charles D Cook and Louis K Diamond (Boston) An extensive study was made of the hemoglobin of one of the affected persons

The venous blood was chocolate brown the color was unaffected by shaking in air Methemoglobin was not increased The color was due to an abnormal pigment On prolonged electrophoresis three zones A B and C could be seen trail

(5) S 126 300 301 A g 16 1957

trate at the periphery with as many as two thirds of all the red cells beneath the outer 25% of the cover slip s area Platelets however are almost randomly dispersed Thus the true ratio of red cells to platelets is not established in the central portions of the cover slip Experimentally when the cover slip and slide are coated with silicone both red cells and

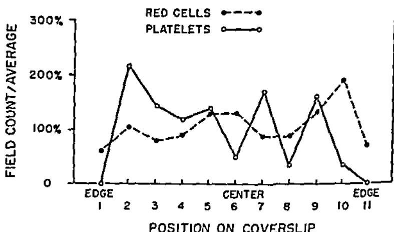



Fig 52 —Ind t platel t o nt D tr but n f ed c ll nd pl telets d op su pend d betwee l c d u fa s Exper me t perf m d n m ll d p Forty f u fi ld w c ted ea h po t p se t 4 fi ld There w 441 red cell and 26 plat lets F ly nd m di t b t on f d c lls (C urtesy f F tch H J Blood 12 671 676 July 1957 )

platelets are almost randomly dispersed (Fig 52) When this is done the indirect count almost equals the direct count

► [So simple when you know why!—Ed ]

Blood Chimerism in Pair of Twins is described by P B Booth Gertrude Plaut J D James Elizabeth W Ikin Phyllis Moores Ruth Sanger and R R Race[4] (London) Each twin has red cells some of which were directly inherited but the rest acquired as grafts in utero from the opposite twin in this instance of different sex The male has 86% $A_1$ and 14% O red cells and also has female drumsticks in some of the polymorphonuclear white cells which must therefore also have been transferred and become grafted in utero The female twin has 99% O cells and 1% A cells The $A_1$ cells are MSMs CDe/cde $Fy^bFy^b$ Jk $Jk^b$ the O cells are MSMS cDE/cde Fy $Fy^b$ Jk Jk in their other groups they do not

(4) B t M J 1 1456 1458 J e 2 1957

tative and accurate Physiologic binding is achieved by incubating radioiron with fresh plasma before administration or by injecting iron citrate Immediate loss may occur if iron binding protein is nearly saturated but the clearance rate is not affected Cohn s fraction $IV_7$ is not suitable for quantitative measurements of plasma iron turnover

The clearance rate can be determined by sampling over a few hours and expressing the result as a single exponential If sampling is prolonged a single value is no longer accurate Apparently a biologic system exists in which plasma iron is in equilibrium with one or more other pools Normal marrow may release back into the plasma as much as 15% of the iron initially taken up by developing red cells and this fraction may increase in certain blood dyscrasias Results calculated from the initial slope of disappearance tend to overestimate the amount of iron being turned over through the plasma because of these factors If within the period of study 90% of the activity is cleared from the plasma without significant deviation from the initial slope the turnover has probably been well approximated If less than 50% has cleared serious error may be introduced by subsequent alterations in slope

The radioiron plasma clearance rate is usually lengthened in aplastic anemia and accelerated with increased erythropoiesis but the results depend on the level of plasma iron Any measure of iron level or clearance rate alone has little meaning

The turnover in iron in other than blood forming tissues may amount to as much as 50% of normal turnover and may double with iron surplus Blood destruction has even less effect on plasma iron turnover Excessive red cell breakdown increases plasma iron concentration but the turnover is not altered significantly Thus body tissues do not accept much iron when the plasma is loaded However changes in marrow activity are rapidly reflected by alterations in plasma iron turnover and erythroid marrow activity probably is the dominant factor in determining plasma iron turnover

Plasma iron turnover was compared with the reticulocyte count per cubic millimeter of peripheral blood in normal subjects and patients with various anemias (Fig 53) Turnover results were consistent in normal subjects and patients with diseases unrelated to the hemopoietic system Patients with the marrow hyperfunction of congenital or acquired

ing the hemoglobin band Zone B was brown In normal persons only a single band is present, parallel to zone A Spectrophotometric studies showed that zone C contained an abnormal oxyhemoglobin and an abnormal methemoglobin After oxidation of the oxyhemoglobin in zone C to methemoglobin no peak appeared at 630 mμ indicating that the methemoglobin differed in its spectrum characteristics from normal methemoglobin

Thus in this second family with methemoglobinemia of the Horlein and Weber type both normal oxyhemoglobin and an abnormal oxyhemoglobin hemoglobin M were identified An abnormal methemoglobin differing in spectrum characteristics from normal is also present The abnormal oxyhemoglobin probably is the precursor of the abnormal methemoglobin and the term methemoglobin M is applied to it The family history indicates that hemoglobin M has a *dominant inheritance pattern as is usual with abnormal* hemoglobins

**Erythrokinetics IV Plasma Iron Turnover as Measure of Erythropoiesis** Tracer technics allow quantitative estimation of the amount of iron passing through the plasma Changes in plasma iron turnover have been assumed to reflect changes in erythropoiesis but the possible effects of red cell destruction and altered body iron stores have not been investigated Thomas H Bothwell Arnold V Hurtado Dennis M Donohue and Clement A Finch[6] (Univ of Washington) studied these three factors in experiments on animals and man in whom the rate of red cell destruction had been altered Radioiron was incubated with fresh plasma and administered *intravenously and the radioactivity of the subjects* plasma was determined at regular intervals thereafter

To calculate the rate of red cell formation the plasma iron turnover and the percentage of radioiron reappearing in red cells must be known However it is impossible to know accurately what point on the red cell utilization curve represents that portion of radioiron which proceeds directly to the marrow as compared with the iron originally taken up by other tissues and later recirculated to the marrow In hemolytic anemias the random destruction of newly formed erythrocytes further complicates such uptake curves

Technics which measure plasma iron turnover are quanti

(6) Blood 12 409-427 M y 1957

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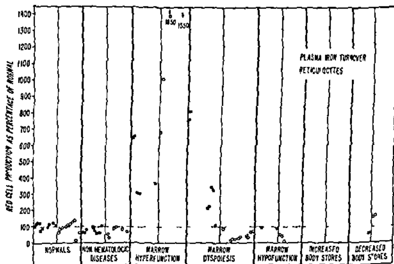
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hemolytic anemia had turnovers 3 6 times normal The reticulocyte index was *usually disproportionately high* In patients with marrow dyspoiesis such as Cooley s anemia and pernicious anemia plasma iron turnover was 2 8 times normal without comparable increase in reticulocytes However in these anemias there is erythroid hyperplasia of the marrow and increased hemoglobin catabolism Thus the plasma iron turnover reflects total erythroid marrow activity both




F g 53 —Pla m on tu ove and et ulecyte c u ts norm l p n nd p t ents w th v r us d s s s (Co rt sy f Bothwell T H *et al* Bl d 12 409 427 M y 1957 )

effective and ineffective whereas the reticulocyte count reflects only effective delivery of viable red cells to the circulation

In patients with severe marrow hypofunction maintained on repeated blood transfusion the plasma iron turnover was normal or reduced in all Most of the plasma iron turnover probably represented redistribution of iron released from hemoglobin breakdown between different body stores Plasma iron turnover within normal limits in any patient with anemia except that due to iron deficiency can almost certainly be regarded as marrow hypofunction

Only 2 of 7 patients with decreased body stores of iron and plasma iron values had decreased plasma iron turnover and

only 1 decreased reticulocytosis These results are inconsistent with previous concepts of impaired hemopoiesis in iron deficiency anemia [and might be explained on the basis that persisting erythropoiesis in the presence of low serum iron would lower it further or that the tracer dose of iron is itself erythropoietically effective—Ed ]

Patients with liver dysfunction myeloid metaplasia and leukemias of different types all with anemias had normal or slightly increased plasma iron turnover and reticulocyte counts Compared with the maximal response of marrow activity seen in hereditary hemolytic anemias of similar severity it is evident that the response of such patients is suboptimal Thus despite a normal or somewhat increased rate of iron turnover the marrow actually shows hypofunction

These results indicate that plasma iron turnover is a simple and useful measure of erythroid marrow activity By correlating it with the reticulocyte count it is possible to indicate whether the marrow activity is effective or ineffective in terms of delivery of red cells to the circulation It is predominantly a measure of marrow erythropoiesis has a high degree of reproducibility and is rapidly responsive to changes in erythroid marrow activity without regard to the viability of the red cells The major difficulty is the lack of a reliable standard for comparison to assess the validity of the plasma iron turnover as a measure of total erythropoietic activity Perhaps correlation with the rate of red cell destruction measured by $Cr^{51}$ labeled cells may completely analyze the red cell production and destruction at a given time

**Studies on Serum Haptoglobin Level in Hemoglobinemia and Influence on Renal Excretion of Hemoglobin** When small amounts of hemoglobin are added to serum weak peroxidase activity can be detected which is present in neither the hemoglobin nor the serum alone A complex of hemoglobin (Hb) and a serum protein haptoglobin (Hp) is responsible and is formed as $HpHb_2$

Carl Bertil Laurell and Margareta Nyman[7] (Malmo Sweden) devised an electrophoretic method for quantitative determination of heptaglobin concentration in serum In normal serum the haptoglobin measured as the quantity of hemoglobin that can be bound varies between 140 and 50

(7) Blood 12 493 506 J 1957

mg /100 ml assuming a molecular weight of 310 000 gives haptoglobin a normal concentration of 1 3±0 5% of the total serum proteins about 0 1±0 04 Gm /100 ml serum

Haptoglobin binds hemoglobin in a firm complex at pH 6 86 and probably does so in vivo during intravascular hemolysis or intravenous administration of hemoglobin Patients with acquired hemolytic anemia and untreated pernicious anemia show no demonstrable serum haptoglobin When hemoglobin is injected intravenously it is found bound to serum haptoglobin in the 10 minute sample (Fig 54) and

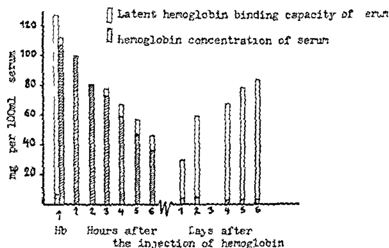



Fig 54—H m gl b b nd ng cap ty f m b fo d aft s t a ou n ject n f h m glot (C u te y f Lau ell C B d Nym n M Blood 1 493 506 Ju 1957 )

if enough hemoglobin is injected all the haptoglobin will be occupied Thus after 24 hours it may no longer be measurable The haptoglobin hemoglobin complex then decreases at a constant rate and may reach levels which are not detectable but it is not excreted in the urine Apparently it is removed by the reticuloendothelial system Haptoglobin measured as the hemoglobin binding capacity of the serum gradually regenerates in succeeding days No free hemoglobin is detectable and no hemoglobinuria appears after intravenous injection unless more hemoglobin has been administered than can be bound by the circulating haptoglobin

The normal hemoglobin binding capacity of haptoglobin is about 90 m /100 ml plasma This is just below s

previously ascribed to the threshold of renal tubular reabsorption This previous work assumed that all hemoglobin in plasma occurs as free hemoglobin As a result the tubular reabsorbing capacity has been overestimated The renal threshold lowering previously found after repeated injections of hemoglobin is actually due to a lowering of the haptoglobin concentration in the plasma Since less hemoglobin is thus bound injections of smaller amounts of hemoglobin become evident as hemoglobinuria Hemoglobinuria is not evident until the amount of hemoglobin administered intravenously or liberated intravascularly exceeds the binding power of the haptoglobin and the reabsorption capacity of the tubules

► [Serum binding of hemoglobin appears to be an important physiologic principle Some observers have not found that electrophoresis of hemoglobin tinged serum shows a specific band corresponding to haptoglobin but "overflow may have obscured its specificity for smaller amounts—Ed.]

**Febrile Transfusion Reactions Caused by Sensitivity to Donor Leukocytes and Platelets** Unexplained febrile reactions accompany more than 1% of all transfusions and occur especially in patients who receive multiple transfusions They have been considered nonspecific because no contamination pyrogens red cell incompatibility or sensitivity to donor plasma has been demonstrable Thomas E Brittingham and Hugh Chaplin Jr [8] (Washington Univ ) detected strong leukoagglutinins in the serum of most patients who received multiple transfusions and had repeated severe febrile transfusion reactions These were typical isoantibodies without activity against the patient s own leukocytes but clumping a wide range of normal donor leukocytes

Five patients who had previously had 20 85 transfusions had histories of repeated transfusion reactions and had demonstrable antibodies against specific normal leukocytes Of these 5 2 had no agglutinins against donor platelets and 2 others had only weak agglutinins Indirect Coombs cross match was performed before each transfusion [and was presumably negative—Ed ] Five other patients who were anemic and required transfusions had no history of transfusion reactions had no leukoagglutinin demonstrable in the serums and were taking no antipyretic antihistamine or steroid medication None of these patients had received more than 7 transfusions previously

(8) J A M A 165 819 8 5 Oct 19 1957

Blood from donors was collected in plastic bags and centrifuged then as much as possible of the buffy coat removed When the rest was transfused no adverse effects occurred in any patient When the buffy coat was given patients who had previously reacted to transfusions had a typical reaction with fever symptoms and characteristic laboratory findings Patients who had not previously had transfusion reactions *reacted to neither the buffy coat nor the sedimented cells*

The pattern of reaction was remarkably consistent an immediate reaction a latent period and a delayed reaction The immediate reaction began within 5 minutes of the start of the transfusion with flush palpitation tachycardia cough choking in the chest and neutropenia The latent period lasted 15 60 minutes The delayed reaction was characterized by a rise in diastolic blood pressure and onset of headache and chilliness progressing to frank rigor, followed by a rapid rise in temperature Apathy irritability probably impaired mentation and prostration persisted several hours A neutrophil leukocytosis with a marked shift to the left reached its peak 2 5 hours after the beginning of the transfusion

One patient was given blood containing leukocytes to which he was sensitive by siliconed syringe technic These were out of the donor s circulation less than 1 minute before being infused The resulting typical severe reaction with shaking chills and fever indicated that processing or storage of white blood cells was not essential to produce the reactions in sensitive patients The reactions can be prevented by removing leukocytes and platelets from the blood to be transfused and giving only the red cell fraction not containing the buffy coat

► [A very practical discovery indeed And so only the purists among us will complain of the authors misuse of the phlebotomist s time honored expression buffy coat This is properly the fibrin mass appearing in the upper part of a blood clot formed after the red cells have rapidly sedimented With the introduction of anticoagulants fibrin was of course no longer seen and so in vulgar usage the supernatant white cells and platelets have become the modern buffycoat —Ed ]

**Unexpected Blood Group Incompatibility Revealed by $CR^{51}$ Labeled Red Cells** P L Adner and S Sjolin[9] (Univ Hosp Uppsala) injected 4 10 ml of labeled ABO and D (Rh ) compatible cells from 15 healthy full term new born infants into 15 healthy adults who had never had

(9) Scand n v J Cl & Lab I v t 9 265 269 1957

a transfusion In 6 experiments the survival curves were quite normal in 4 the curves followed an approximate exponential course but shorter than normal and in 5 the curves first showed a normal course but after 5 15 days a change was evident and most of the tagged cells vanished in a short time In 4 tests in 1 such recipient (Fig 55) fetal

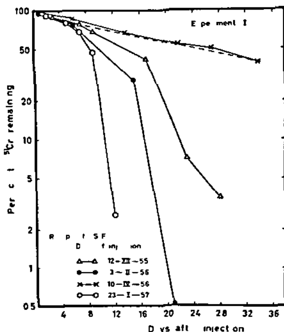



Fig 55 —Rat f disappe ce f C l bel d d ll jected t differ t t m t m p ent Δ—Δ fetal ed lls ●—● nd O—O d ll f m m l d lt d X—X ec r t wn ed cell b ken h g ppa ent rvi l f t f sed ed ll f rmal d lt (Court sy f Ad er P L and Sj l S Sea d J Clin & Lab I t 9 65 269 1957)

red cells and adult donor red cells showed abnormal survival though his own cells tagged and reinjected survived normally

In 15 other tests compatible cells from 15 healthy adults were tagged and injected into 15 other healthy adults In 12 survival times were normal but in 3 a sudden break was found between 9 and 18 days When second transfusions were given 2 and 5 months later from the same donors the tagged red cells were rapidly destroyed In the serum of 1 recipient

an antibody against factor E(rh ) was discovered just be fore the second transfusion and another had an antibody against the Duffy system (anti Fy ) 12 days after the second transfusion

Although antibodies were found in only 2 recipients these abnormal survival curves most likely represent immuniza tion Homotransfusion probably induces immunization more commonly than is generally appreciated Most of these pa tients show no conspicuous clinical symptoms Such immu nization may explain why repeated transfusions to a recip ient are often less and less effective The findings stress the relative inefficiency of the usual compatibility tests before a transfusion

► [Obviously compatibility tests have limitations but are necessary as a screen against disaster The clinical experience of these authors confirms that of Jandl and Greenberg (J Lab & Clin Med 49 233 1957) —Ed.]

**Intravenous Infusion of Bone Marrow in Patients Receiving Radiation and Chemotherapy** In experimental animals after a lethal dose of radiation the bone marrow may be re populated by intravenous infusion of cellular suspensions of marrow taken from healthy isologous homologous or in some heterologous donors E Donnall Thomas, Harry L Lochte Jr Wan Ching Lu and Joseph W Ferrebee[1] collected bone marrow from fetal and adult cadavers ribs removed at surgery and from aspiration biopsy specimens of the ilium It was then passed through a stainless steel screen and broken into a smooth suspension and the fat was removed by centrifugation The cells were resuspended in tissue cul ture fluid and serum and then administered intravenously or frozen in glycerol and stored at −80 C

Six patients received intravenous infusions of marrow cells Evidence for growth of the marrow homograft was apparent in 2 Prolonged or permanent takes occurred only after radiation sufficient to produce bone marrow aplasia The injections were apparently sterile since no reactions occurred and septicemia was not demonstrable Pulmonary emboli did not occur probably because the screen syringe technic was effective

Human bone marrow can be collected and stored in sig nificant quantities and can be administered with safety After administration it may grow even under disadvanta geous competitive circumstances in incompletely irradiated

(1) N w E gland J Med. 257 491-496 Sept 12 1957

hosts who have marrow neoplasia In the atomic age the possibility of radiation damage to marrow has increased Infusion of marrow into mice or monkeys can induce recovery after doses of radiation which otherwise would be lethal However immune reaction to foreign marrow leading to increased mortality occurs in irradiated rodents either as a reaction of the graft to the host or of the host to the graft or both Nitrogen mustard may induce survival of marrow homografts in rodents when used in near lethal dosage but the effect is not easily demonstrated Thus marrow homografts may have little usefulness in attempts to restore hemopoiesis after toxic chemotherapy

It is possible that such technics will be applicable to man if sufficient radiation is given to suppress the host immune reaction by accident or design

Man 59 with chronic lymphatic leukemia progressively did not respond to x ray therapy or triethylene melamine Hemoglobin was 2 9 Gm / 100 ml and the white blood cell count over 600 000 He was given a total of 450 r of whole body radiation over 8 days followed by intravenous infusion of bone marrow He was type O C (−) Bone marrow was obtained from a patient with type O C (+) who died of cerebral hemorrhage Ribs were removed sterile within 2 hours of death suspended in tissue culture fluid and passed through coarse and fine screen syringes and the fat was removed by centrifugation The suspension was mixed with an equal volume of 30% glycerol and frozen within 3 hours of death

The marrow was stored at −80 C for 3 weeks Cultures were negative It was then thawed the osmolarity reduced and the marrow given intravenously on 3 successive days a total of 3 000 million cells Thereafter there was progressive appearance of circulating erythrocytes of the donor type which subsequently disappeared This probably represented a temporary take of the homograft suggesting a temporary impairment of immune response and a satisfactory dose of donor marrow

The material presented indicates the complexity of the problem of marrow transplantation with its unknown quantities and potential hazards

► [Already families of patients or their doctors are inquiring about the possibility of homologous marrow transplants in blood dyscrasias Judging from the experiments in animals at the moment a patient with a potentially fatal leukemia who survived the heavy general radiation required might accept a bone marrow graft successfully for a time Whether the procedure would prolong or shorten his life and whether it would lessen or add to his misery is problematic At present this field requires far more exploration and resolution of its basic problems in animals before clinical investigation to say nothing of therapy appears to be appropriate That frozen and thawed human marrow will survive and grow suggests that a reserve of frozen isologous marrow might have practical value in case of accidental overdosage of the patient by radiation or chemotherapy —Ed ]

**Determination of Sites of Red Cell Destruction Using $Cr^{51}$ Labeled Cells** After injection of the subject s own red cells which had been incubated with $Cr^{51}$ N C Hughes Jones and L Szur[2] (London) found the highest counts in normal subjects to be over the heart spleen and liver The findings were similar in 4 patients who had splenomegaly due to portal hypertension but normal red cell survival

Patients with hemolytic anemia can be divided into three groups In group I the accumulation of $Cr^{51}$ in the spleen and liver are within normal range In these patients hemolysis is intravascular and no benefit can be expected from splenectomy An example is paroxysmal nocturnal hemoglobinuria In group II the excess of counts over the liver is within normal range but the excess of the spleen is marked These patients will benefit from splenectomy Examples of this type are hereditary spherocytosis hemolytic anemia secondary to leukemia and primary hypersplenism In group III excessive uptake in the spleen and liver is demonstrable as marked excess of counts over these areas Such patients will derive only partial benefit from splenectomy

► [For details the reader should consult the original and such other articles as those of Schloesser *et al* (J Clin Invest 36 1470 1957) Harris *et al* (Brit J Haemat 4 97 1958) and Jandl *et al* (J Clin Invest 35 842 1956 1957 58 YEAR BOOK p 242) These articles concur in suggesting that active splenic sequestration of labeled cells correlates with a beneficial effect of splenectomy

The next article attempts to analyze some of the factors causing splenic sequestration of red cells in so called autoimmune hemolytic anemias — Ed ]

**Destruction of Red Cells by Antibodies in Man I Observations on Sequestration and Lysis of Red Cells Altered by Immune Mechanisms** James H Jandl A Richardson Jones and William B Castle[3] (Harvard Med School) labeled red cells with $Cr^{51}$ and measured survival times and the sites of sequestration in living subjects Some of these were normal adults who had been accidentally isoimmunized through transfusion or pregnancy

ABO incompatible normal red cells in subjects who had normal agglutinin titers or low concentrations of i ohemoly-

(2) B t J H em t 3 3 0 331 1957
(3) J Cl In t 36 14 3 1459 Octobe 1957

sins disappeared from the circulation within 2 minutes of injection Radioactivity was high over the liver but not over the spleen thorax or lumbosacral areas and appeared even faster than when labeled hemoglobin had been injected Excretion of $Cr^{51}$ in the urine was prominent but there was no hemoglobinuria When ABO incompatible cells were injected into subjects who had normal isoagglutinin titers but no isohemolysins the $Cr^{51}$ and the hemoglobin of the circulating plasma rose immediately but to lower levels than in the former group In subjects with high concentrations of isohemolysins hemoglobinemia was abrupt and marked reaching a maximum in less than 60 seconds

Subjects with high titers of incomplete anti D antibody in whom $Cr^{51}$ labeled type D red cells were injected rapidly removed them from the circulation Radioactivity over the spleen was moderate over the liver less When the recipient s serum contained agglutinating as well as incomplete anti C antibodies red cell sequestration was more rapid and hepatic radioactivity more pronounced

$Cr^{51}$ labeled D positive normal red cells were sensitized in vitro with incomplete anti D antibodies and reinjected into the donor or into an ABO compatible normal subject Half were removed in an average of 26 minutes with rapid almost total splenic filtration Red cell agglutinates and chains were frequently visible in the recipient s peripheral blood When D negative red cells were used survival in vivo was not affected $Cr^{51}$ labeled red cells from the cord blood of erythroblastotic infants when injected into ABO compatible normal adult subjects were rapidly removed with evident splenic sequestration and only slight hemoglobinemia Between 25 and 30% of the red cells survived normally In a splenectomized patient red cells sensitized with incomplete anti D serum had a much longer half survival time and uptake of $Cr^{51}$ by the patient s liver was more pronounced Hyperglobulinemia in multiple myeloma resulted in marked reduction of the half survival time of sensitized red cells and of those from acquired hemolytic anemia Only a small fraction of the hemoglobin released from the sequestered red cells escaped into the plasma Total serum bilirubin first increased about 1 hour after injection direct acting bilirubin 2 3 hours later

Injection into a normal subject of red cells previously

sensitized with potent incomplete anti D antibodies leads to rapid almost total filtration of these cells by the normal spleen The same follows injection of anti D sensitized D positive red cells into D negative recipients indicating that the normal mechanisms for filtering these cells do not require a specific immune interaction between cell coating and filter Rather the spleen appears to act passively as a highly efficient filter The quality and quantity of antiserum in the red cell sensitization are critical

The brisk and peculiar fashion in which the normal spleen filters sensitized red cells without intravascular hemolysis suggests a physical or physicochemical mechanism involving the surfaces of the red cells rather than changes within them The size and shape of red cells and the viscosity of their suspensions in native plasma are unaltered by sensitization with incomplete antibodies

Concentrations in vivo of those substances which cause rouleaux in vitro notably fibrinogen and other globulins are critical to the sequestering mechanism Red cell agglutination is an intermediate step in the destruction of sensitized cells After sequestration by nonhemolytic antibodies sensitized red cells are hemolyzed within a few minutes the released hemoglobin is converted to bilirubin within 1 2 hours and the derived iron is available to the bone marrow for reuse within 6 8 hours

There are several mechanisms by which red cells are destroyed by antibodies Intravascular hemolysis occurs by combination of the red cell with the hemolysin antibody in the presence of complement So called extravascular hemolysis is different The complete agglutinin leads to sequestration and destruction mostly in the liver and lungs and less in the spleen The incomplete agglutinin by sensitization leads to rouleaux formation in the presence of fibrinogen or other globulins then to agglutination sequestration (more marked in the spleen) and hemolysis of the cells by lytic factors probably of local tissue origin

Syndrome of Hypogammaglobulinemia Splenomegaly and Hypersplenism Two cases with hemolytic anemia and pancytopenia are reported by Ananda S Prasad E Reiner and C J Watson[4] (Univ of Minnesota) Deficiencies in gamma globulins may be physiologic or transient in infants

(4) Blood 12 9 6 932 Oct ber 1957

congenital or acquired In the congenital and acquired types the failure is not complete since small amounts of gamma globulin can be demonstrated by sensitive technics

Woman 65 had 12 episodes of pneumonia in 7 years Anemia and splenomegaly had not responded to liver therapy $B_{12}$ or iron In September 1955 the hemoglobin was reported as 10 7 Gm /100 ml leukocytes 4 650 and reticulocytes 7.2% Prednisone was started in December between March and August 1956 she received 25 trans fusions 11 of them in the 16 days before admission.

On admission in August 1956 she had tachycardia mild fever purpura icteric scleras bilateral basilar rales an enlarged heart hepato- and splenomegaly and peripheral edema Anemia with 4.2 Gm hemoglobin and 5 4% reticulocytes leukopenia and thrombo cytopenia were marked Coombs test was negative The total serum protein value was 4 5 Gm /100 ml albumin 3 3 Gm and globulins 1 2 Gm The alkaline phosphatase level was 17.2 King Armstrong units Fecal urobilinogen was elevated and serum iron normal Pa per electrophoresis revealed albumin 3.2 Gm alpha$_1$ globulin 0 4 Gm alpha$_2$ globulin 0 5 Gm beta globulin 0 7 Gm and gamma globulin 0 6 Gm /100 ml (normal gamma globulin 1 1 Gm /100 ml ) The distinctly low value despite recent blood transfusions indicated ac quired hypogammaglobulinemia Splenectomy disclosed no evidence of leukemia and corrected the pancytopenia Thereafter hemoglobin was not below 11 5 Gm /100 ml The patient was advised to have in jections of gamma globulin at intervals of 3 weeks In October 19 6 bilateral pneumonia developed and she died Permission for autopsy was not obtained

It is reasonable to presume that as a result of hypogamma globulinemia and resultant repeated infection reticulum cell hyperplasia resulted This caused splenomegaly and hyper splenism This syndrome is relatively common (17 cases) in comparison with the incidence of the total number of cases of acquired hypogammaglobulinemia reported in the literature so far Serum gamma globulin levels should be de termined in patients who have unexplained hepatospleno megaly hypersplenism and hemolytic anemia Splenectomy results in marked hematologic improvement

► [Further evidence that hypersplenism is the result of many causes pro vided only that the filtering function of the spleen for the morphologic elements of the blood is increased.—Ed ]

**Hemoglobin Tolerance in Various Types of Anemia** To determine whether the cells of the reticuloendothelial sys tem could adapt to or compensate for destruction of red cells by increasing hemoglobin metabolism or by converting it to another form Shu Chu Shen[5] (Tufts College) infused hemoglobin solution by a predetermined schedule into 18

(5) A M A A h I t. M d. 101 315 325 F bru ry 1958

hemolytic and 18 nonhemolytic patients During the 1st hour 0 325 Gm hemoglobin was administered at a rate of 5 4 mg/minute or that amount of hemoglobin destroyed by a normal person in 24 hours Thereafter the amount of hemoglobin solution infused during each hour was increased by 0 325 Gm at the beginning of each subsequent hour so that at the end of 5 hours 5 29 Gm hemoglobin had been administered

All patients with hemolytic disease except those with paroxysmal nocturnal hemoglobinuria sickle cell anemia or Cooley s anemia had either a positive Coombs test increased mechanical fragility or shortened survival for transfused cells At the end of the hemoglobin infusion, 16 of these 18 patients had increases in plasma hemoglobin values of between 10 4 and 32 9 mg/100 cc Two with paroxysmal nocturnal hemoglobinuria and initial plasma hemoglobin values of 36 4 and 12 5 mg/100 cc had increases of 89 5 and 50 2 mg Patients of the nonhemolytic group and those without anemia showed increases above 35 mg

Plasma hemoglobin disappeared rapidly after the infusion was terminated and was normal 19 hours later If the plasma hemoglobin value increased less than 35 mg/100 cc hemoglobinuria did not occur in those with hemolytic disease In 1 patient with no hemolytic disease the plasma hemoglobin value increased to 100 9 mg/100 cc at the end of infusion but no hemoglobinuria was noted Patients who excreted hemoglobin did not necessarily have a high value of plasma hemoglobin Those who showed no hemoglobinuria had normal urine those with hemoglobinuria invariably had albuminuria and hemosiderinuria and some had hemoglobin casts

Plasma indirect bilirubin levels increased in all patients during or after infusion varying from 0 1 to 1 6 mg/100 cc in the hemolytic group and from 0 1 to 0 7 mg in the nonhemolytic group The 2 patients with paroxysmal nocturnal hemoglobinuria who had marked hemoglobinemia and hemoglobinuria after infusions showed only minimal increases in plasma indirect bilirubin level

The high tolerance for hemoglobin in patients with chronic hemolytic anemia suggests that removal of plasma hemoglobin is accelerated in some way through the reticuloendothelial system Unless the daily destruction of red blood cells

exceeds 3 5 times the normal destruction hemoglobinemia will not be detected without a colorimeter quantitative de termination This may explain the clinical observations of absence of hemoglobinemia in such patients Plasma indi rect bilirubin levels increase in all patients after infusion of hemoglobin and to somewhat higher levels in patients with liver disease

**Autoimmune Hemolytic Anemia II Morphologic Ob servations and Clinicopathologic Correlations** Henry Rap paport and William H Crosby[6] (Armed Forces Inst of Pathology) studied 50 cases correlating clinical and hema tologic findings with the histology of the spleen The diag nosis of acquired autoimmune hemolytic anemia had been established in each Of the 50 spleens 41 had been removed surgically and 9 were obtained at autopsy Fourteen were associated with malignant lymphoma Spleens from 28 pa tients with hereditary spherocytosis and 3 with familial non spherocytic hemolytic disease were studied for comparison

The principal changes in autoimmune hemolytic anemia were found *in the spleen but were not uniform* Variations were primarily due to differences in congestion of pulp cords and sinuses and the presence or absence of extramedullary hemopoiesis The architecture was preserved but modified In 18 of the 50 spleens the cords were severely congested in contrast to the sinuses which either were empty or con tained only small to moderate numbers of red blood cells (table) The histology in these spleens resembled that seen in hereditary spherocytosis In 21 others congestion was equal in the cords and sinuses and in 11 the sinuses were congested and the cords narrow

The degree of congestion of splenic cords and sinuses was positively correlated with the osmotic fragility and the pres ence of spherocytosis (table) Cells lining the splenic sinuses were prominent similar to the findings in hereditary sphe rocytosis Erythrophagocytosis was observed in four fifths of the spleens It may have been masked in the others be cause of heavy congestion of the cords Extramedullary hemopoiesis was found in 15 spleens predominantly the erythrocyte series Hemosiderin deposition was abundant

Lymph nodes were available for study in 14 cases and re vealed hemosiderosis and erythrophagocytosis though less

(6) *Am J P th 33 4 9 437 M y J 1957*

marked than in the spleen Extramedullary hemopoiesis was observed in 2 Bone marrow sections showed erythroid hyperplasia in 10 of 13 cases of idiopathic autoimmune hemolytic anemia The liver showed marked hemosiderosis in parenchyma and Kupffer cells

*Spleens from patients with congenital nonspherocytic hemolytic disease* showed almost complete absence of red blood

RED BLOOD CELL CONTENT OF SPLENIC CORD AND SINUSES IN RELATION TO SPHEROCYTOSIS IN SPLEENS IN WHICH CORDS WERE SEVERELY CONGESTED AND RED BLOOD CELL CONTENT OF SINUSES NOT SIGNIFICANTLY INCREASED

| Accessio umbe | Sph ocytosis | Osm fragil ty | Red blood cell content | |
|---|---|---|---|---|
| | | | Cord | Sinuses |
| 3 4905† | + | Marked increase | ++++ | O |
| 166580 | + | Ma ked u crease | ++++ | + |
| 211621†‡ | + | Marked increase | ++++ | + |
| 2902 3 | + | Marked crease | ++++ | + |
| 490583 | + | Ma ked i crease | ++++ | + |
| 500865 | + | Marked increase | ++++ | + |
| 126304‡ | | | ++++ | ++ |
| 234089 | O | Norm l | ++++ | ++ |
| 68756 | + | Marked i re se | ++++ | ++ |
| 30 465‡ | + | Marked increase | ++++ | ++ |
| 550856 | + | Moderate increase | ++++ | ++ |
| 575449 | O | Normal | ++++ | ++ |
| 495207 | | | +++ | + |
| 499 5 ‡ | + | Slight increase | +++ | + |
| 5418 3 | + | Slight increase | +++ | + |
| 543491 | O | Normal | +++ | + |
| 593 62 | + | Normal | +++ | + |
| 609537 | + | M rk d increase | +++ | O |

No mal 0 02 or l bo e no m l cont ol sl ght nc ase 0 03 0 05 bo e n mal cont ol mod t nc e e 0 06-0 08 bove n rm l cont ol m rk d r e 0 09 o mo e above rmal c t l
†Pat ts w th mal gna t lymph ma
‡Spleens bta ned at a topsy

cells in the cords Congestion of splenic cords is not pathognomonic of congenital hemolytic anemia nor is the absence of such a picture indicative of an acquired form Its presence or absence merely indicates whether *the hemolytic disease* is predominantly spherocytic or nonspherocytic In contrast congested sinuses with few red blood cells in the cords were invariably seen in patients without spherocytosis These observations suggest that congestion of the splenic cords in autoimmune hemolytic anemia is due largely to selective retention of morphologically abnormal red blood cells [or that the sensitized *cells become spheroidal because they* are retained—Ed ]

Selective retention of spherocytes in the splenic cords

contributes to the anemia However comparison of patients with and without spherocytosis showed no difference in hematologic response or longevity after splenectomy ✓

► [In view of the correlation between active splenic sequestration of labeled red cells and beneficial effects of splenectomy this last is surprising —Ed ]

**Inborn Errors of Metabolism in Red Cells of Congenital Hemolytic Anemias** are reviewed by T A J Prankerd[7] (Univ of London) Metabolism in the mature red cell is predominantly glycolytic Energy gained from anaerobic breakdown of glucose is stored as adenosine triphosphate and ultimately coupled to a number of dependent reactions of which the maintenance of electrolyte fluxes and membrane structure are vital for cell survival Red cell metabolic abnormalities have been reported only in hereditary spherocytosis and congenital nonspherocytic hemolytic anemias not in thalassemia or hemoglobinopathies

In hereditary spherocytosis glucose consumption and radiophosphorus exchange are normal but a basic intracellular defect in phosphorylation is present In many patients the changes are reversible if a nucleoside is provided as an alternative substrate for metabolism In contrast to normal cells the highest activities are found in the inorganic phosphate pools whereas activity in the 2 3 diphosphoglycerate and adenosine triphosphate pools is lower than normal No specific enzyme defect has been located but it appears to be inherent in the cell since it is detected in the cells of patients of all ages and persists after splenectomy It has been suggested that the enzymes are activated by magnesium ions The observed changes could be due to a single enzyme abnormality and might also be present in all cells of the body But the red cell being the only cell entirely dependent on glycolysis would be the most vulnerable to such defects Since such red cells pass sluggishly through and stagnate in the splenic pulp the resulting hemoconcentration could create conditions which would reduce the glucose to the cell The cells being incapable of glycolysis could no longer maintain their chemical stores of energy so hemolysis would ensue

Of 4 patients with nonspherocytic hemolytic anemia 3 had gross defects in red cell metabolism with a low content of adenosine triphosphate deficient glucose consumption

(7) Am J Med 22 724 729 May 1957

and decreased exchange of phosphorus Perhaps the non spherocytic hemolytic anemias can be divided into those which show metabolic abnormalities and those which do not

In Negroes who acquire anemia after primaquine administration *the red cells lack the enzyme glucose 6-phosphate* dehydrogenase responsible for oxidizing glucose 6 phosphate to 6 phosphogluconate This is a further example of an inborn metabolic error in erythrocytes

► [In studying the next 3 articles the reader would do well to reflect that the antigens responsible for the so called autoantibodies have never been defined The conditions discussed may then be viewed with less prejudice as disorders in which the red cells are coated with protein whether developed in response to an antigen or not At any rate most of the phenomena said to characterize these autoantibodies can be produced by coupling serum proteins to the cell surface by non immunologic means as described by Jandl and Simmons (Brit J Haemat 3 19 1957 1957 58 YEAR BOOK p 223) —Ed ]

***Serology of Autoimmune Hemolytic Disease*** **Observations on 41 Patients** are reported by Robert S Evans and Russell S Weiser[8] (Univ of Washington) Improved serologic technics in the past 10 years have sought successfully for evidence of antibody adsorbed cell surface rather than free in the plasma and have characterized the antibodies of acquired hemolytic anemia though the genesis is still unclear The antibodies resemble the isoantibodies evoked by incompatible transfusions and maternal fetal incompatibility except for their unique property of autoactivity [They also differ in their ease of elution and panagglutinating ability —Ed ]

Exposure of normal cells to trypsin is valuable in detecting the free serum antibody of acquired hemolytic anemia The antiglobulin technic (Coombs test) is the most sensitive and reliable method It employs antibodies against human serum proteins produced in animals to reveal iso and auto antibodies on the cell surface The cells must be washed free from plasma and in a positive test are agglutinated In the direct test the patient s red cells are tested in the "indirect normal red cells are tested after incubation in the patient s serum Other methods of detecting antibody coated red cells employ 30% beef albumin in serum [Glue fibrinogen or polyvinyl pyrrolidone are better —Ed ]

Warm antibodies more active at 37 C than at lower temperatures are gamma globulins in most cases Cold anti

(8) A M A Arch I t M d 100 371 399 S pt mber 1957

bodies most active at low temperatures are composed of proteins other than gamma globulin Though the antibodies of autoimmune hemolytic disease have the peculiar property of autoactivity they are not specific for the red cells of the patient with the disease but combine readily with normal red cells They are species specific They do not combine with or damage other tissues

Of the 41 patients with autoimmune hemolytic anemia 19 had associated diseases including leukemia virus infections trauma and diseases of unknown etiology The red cells of 37 were Coombs test positive The direct antiglobulin test may be negative in a few patients who have other features of autoimmune hemolytic disease False negative reactions appear to be due to technical factors such as prozoning or the reversal of agglutination with incubation but in some patients are probably due to lack of antibody in the anti globulin serum specific for the molecular species of plasma protein sensitizing the patient s cells Patients with auto immune hemolysis who had high titers of cold agglutinins had persistent sensitization of their red cells at body tem perature and continuous acceleration of blood destruction even though warm Incomplete antibody adsorbed to the cell surface may be more active at temperatures below 37 C Free serum antibody similar to that on the cell surface was not detectable at body temperatures indicating that adsorp tion was fairly complete

Two patients had hemolytic antibodies In 1 the autoanti bodies produced hemolysis in vitro of all types of human red cells through action of complement The other hemo lyzed the patient s cells only in the presence of anticoagu lants *known to remove calcium and magnesium ions*

Free serum antibody could not be demonstrated in vitro in many patients though they had active autoimmune he molysis Concentration in serum may depend on the amount produced and the degree of saturation of red cell recep tors Autoantibody appears to be continuously dissociated from the cell surface and perhaps an association dissociation equilibrium exists which may vary with different antibodies and antigens influencing the serum antibody concentration

Temperature variations between 5 and 37 C have a varia ble effect on the activity of free serum and eluted antibodies Those antibodies composed of gamma globulin show

greater activity at 37 C than at lower temperatures Variation in pH between 6 6 and 8 had little influence on the union of autoantibody with red cell antigens At present there is little knowledge about the relation between the in vitro serologic characteristics of autoantibodies and their in vivo role in accelerated blood destruction

► [This valuable article should be studied in the original Even so the last statement in this abstract will perhaps no longer appear to be entirely so to readers of the original of the second article in this section that by Jandl *et al*—Ed ]

**Autoimmune Hemolytic Anemia Arrested by Removal of Ovarian Teratoma Review of Literature and Report of Case** are presented by Kevin G Barry and William H Crosby[9] (Walter Reed Army Inst of Res )

Nurse 26 Negro had no history of hemolysis One year earlier she began having chronic fatigue generalized myalgia headache palpitation and exertional dyspnea Six months later she noted scleral icterus and dark urine She was given multiple transfusions without improvement She was then placed on 40 units of ACTH daily but despite this therapy required 1 3 blood transfusions weekly

Examination revealed steroid facies and obesity moderate icterus and pallor a blowing basal systolic murmur a palpable liver edge and a spleen down 3 cm An irregular 10×8 cm mass was palpated in the right pelvis The hematocrit was 26 and the reticulocyte count 26% Osmotic fragility was increased A sickle cell preparation showed 80% sickling Serum bilirubin was 2 2 mg / 100 ml Bone marrow aspirates showed marked erythroid hyperplasia Direct and indirect Coombs tests were positive and warm agglutinins were demonstrated The diagnosis was autoimmune hemolytic anemia Within 5 hours of infusion of labeled red cells 60% were destroyed A teratoma of the left ovary was removed Thereafter the peripheral blood remained normal without further therapy the spleen shrank beneath the costal margin but the direct Coombs test remained positive The spherocytosis and hemolysis disappeared

This is the tenth reported case in which autoimmune hemolytic anemia has been associated with an ovarian tumor or a dermoid elsewhere in the body (table) In 6 removal of the teratoma cured the hemolytic anemia Precise diagnosis is important since splenectomy can cure hereditary spherocytosis but not necessarily this condition (table Cases 1 3 and 5) whereas teratomectomy can cure this type of symptomatic hemolytic anemia Steroid therapy with or without splenectomy for autoimmune hemolytic disease offers insecure remission in only 50% of such cases The blood condition is cured by teratomectomy if a teratoma is associated with the hemolytic process

(9) A n I t Med 47 100 1007 Novembe 1957

DATA FROM CASE REPORTS* OF AUTOIMMUNE HEMOLYTIC ANEMIA ASSOCIATED WITH TERATOMAS

| Author | Age in Years 1 | [illegible] 2 | [illegible] 3 | Palpable Tumor 4 | [illegible] 5 | [illegible] 6 | [illegible] 7 | [illegible] 8 | [illegible] 9 | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 [illegible] 1938 | 4 | 2 m | × | + | 3 6 | + | 45 5 | + | + | [illegible] |
| 2 [illegible] 1939 | 19 | 2 y | 0 | + | 5 | 0 | 15 | + | + | [illegible] |
| 3 [illegible] 1941 | 47 | 5 m | + | + | 5 1 | + | 46 | + | × | [illegible] |
| 4 [illegible] 1945 | 35 | 1 m | × | + | 5 | + | 10 | + | + | [illegible] |
| 5 [illegible] 1950 | 40 | [illegible] | + | + | 4 3 | × | 16 | + | + | [illegible] |
| 6 Allibo[illegible] C[illegible] 1951 | 5 | 3 m | × | + | 7 | + | 39 | + | 0 | [illegible] |
| 7 [illegible] 1954 | 61 | [illegible] m | 0 | 0 | 5 2 | + | 20 | + | × | [illegible] |
| 8 [illegible] 1955 | 26 | 1 y | + | + | 3 6 | + | 58 | + | + | [illegible] |
| 9 [illegible] 1956 | 73 | 13 y | + | + | RBC 1 2 mil | + | [illegible] | + | × | [illegible] |
| 10 [illegible] | 30 | × | + | + | 5 8 | + | 60 | + | + | [illegible] with ACTH [illegible] Coombs [illegible] |

[illegible]

**Serum Proteins in Acquired Hemolytic Anemia (Autoantibody Type)** W N Christenson and J V Dacie[1] (Postgrad Med School London) studied 85 cases classified as idiopathic or secondary and with respect to whether the autoantibodies were of the warm or cold type

Serums from patients with warm autoantibodies showed no characteristic pattern on electrophoresis The mean concentrations of albumin and alpha and beta globulins were lower than the normal means and the mean gamma globulin concentration was slightly elevated There were occasional individual elevations in gamma globulin particularly in patients with disseminated lupus erythematosus or macroglobulinemia

Serums from patients with cold antibodies had markedly abnormal patterns Of 10 serums containing cold agglutinins at titers greater than 8 000 at 4 C 9 presented a homogeneous pattern with an abnormal peak in the $gamma_1$ region Serums from patients with hemolytic anemia following virus pneumonia or paroxysmal cold hemoglobinuria showed a rise in the alpha and gamma fractions typical of infective disease

Cryoglobulins were present in some serums Several serums with obvious $gamma_1$ peaks contained cryoglobulin which had a mobility identical with that of the peak

A $gamma_1$ peak was consistently found in patients with chronic hemolytic anemia hemoglobinuria or Raynaud s phenomenon Evidence suggests that the peaks in the serums of some of these patients is largely composed of antibody globulin Sometimes the antibody protein exists in the form of a cryoglobulin All diseases in which cryoglobulins have been found involve disturbances in the growth of the cells of the reticuloendothelial system and abnormal antibodies sometimes characterized by a peak in the $gamma_1$ region could also arise from this cause

► [Because cryoglobulins have not been produced experimentally as a response to antigens we may further question the propriety of their description as antibody proteins —Ed ]

**Genetic Study of a Defect in Glutathione Metabolism of Erythrocyte** Two discrete variants in a population suggests a genetic origin This hypothesis is further supported if the variation is limited to one racial group These circumstances

(1) B t J H em t. 3 153 164 195

prevail in the intrinsic defect of erythrocytes unusually sensitive to hemolysis by primaquine in vivo in certain Negroes Incubation of such cells with acetyl phenylhydrazine (APH) causes an abnormal number of Heinz bodies to appear and the content of reduced glutathione (GSH) to be markedly reduced The test for reduced glutathione (glutathione stability test) is a standard sensitive method for detecting susceptible persons The abnormality is considered to be loss of activity of the enzyme glucose 6 phosphate dehydrogenase which catalyzes a reaction providing reduced triphosphopyridine nucleotide (TPN) To maintain glutathione in the reduced state in the erythrocyte TPN is required In the absence of sufficient reduced TPN the protective potentialities of the GSH may be overcome by primaquine or other substances [oxidants—Ed ] and the metabolism of the cell adversely altered This inborn abnormality of the erythrocyte predisposes to hemolytic anemia after administration of primaquine sulfanilamide acetanalid and certain other drugs The in vitro effects of naphthalene and its metabolic derivatives of nitrofurantoin of fava beans and of vitamin K on the abnormal red cells indicate that the same mechanism may be involved in producing hemolytic anemia by these agents

Barton Childs William Zinkham Eugene A Browne Exall L Kimbro and John V Torbert report observations on the distribution of this red cell defect in the population and within families which support the hypothesis that it is associated with the presence of a single mutant gene in the genotype of an affected individual

Negroes randomly selected from the medical and pediatric outpatient departments were studied to determine the frequency of primaquine sensitive persons None were seriously ill The glutathione stability test was used Among males the incidence of sensitive persons or reactors was 14% compared with about 2% in females Another 5% of females showed partial sensitivity and were called intermediates

The same test was applied to relatives of the reactors There were more reactors among males but a pool of female reactors and intermediates showed nearly as many females as males Relatives who were affected appeared in as many

(2) B ll J h H pk H p 10 21 37 J ry 1958

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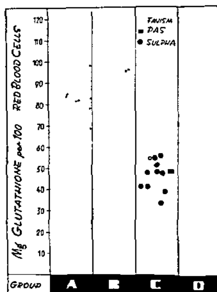
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(1) B r J H m t 3 153 164 1957

sulfonamides (Fig 56) and was a frequent finding in the relatives of affected persons

The findings suggest that a constitutional anomaly of erythrocytes glutathione deficiency is essential for the pathogenesis of these acquired hemolytic conditions The glutathione deficiency is not a result of hemolysis but precedes it It apparently is hereditary The cause of the gluta




Fg 56—Cl tath ont t f blood g o p (Co rt sy f S be g A t l Blood 12 603 612 July 1957)

thione deficiency of erythrocytes is unknown No apparent defect in the mechanism of reducing glutathione was found

**Drug Dependent Coombs (Antiglobulin) Test and Anemia Observations on Quinine and Acetophenetidin (Phenacetin)** are presented by E E Muirhead E R Halden and M Groves[4] (Southwestern Med School) The Coombs test for erythrocytes has been valuable in isoimmune states and autoimmune acquired hemolytic anemia Repeated contact with the trivalent antimony compound stibophen has caused hemolytic anemia In vitro and in vivo the patient s plasma plus stibophen caused red cell agglutination and a

(4) A.M A A h I t Med 101 87 96 J ry 1958.

as three generations which suggested genetic determination

The most likely hypothesis for the mode of inheritance is that a sex linked gene with incomplete dominance expressing itself variably in heterozygotes is capable of controlling the characteristic

The members of two families with hemolytic episodes following ingestion of fava beans were examined by the glutathione stability test Both affected members and their relatives were reactors The distribution of the defect within the families suggested that it too was associated with a sex linked gene showing incomplete dominance and variable expression

► [See also the following article --Ed ]

**Studies on Erythrocytes in Cases with Past History of Favism and Drug Induced Acute Hemolyt c Anemia** Most cases of acquired hemolytic anemia and all cases of thalassemia show an ethnographic distribution Only Sephardic Jews originating from oriental and Mediterranean countries whose complexion is darker than that of Jews from eastern central and western Europe, are subject to such hemolytic disturbances Such distribution suggests a common constitutional factor to explain the gross blood destruction after ingestion of fava beans or specific agents such as sulfonamides plasmoquine or PAS or after some infections Investigations by others have proved the existence of erythrocytes abnormally sensitive to primaquine and other aniline derivatives in about 10% of American Negroes

A Szeinberg C Sheba Nina Hirshorn and Eva Bodonyi[3] (Tel Hashomer Israel) investigated four groups of persons group A light complexioned Ashkenazic Jews from eastern central and western Europe who had no hemolysis group B dark complexioned Sephardic Jews who had no hemolysis group C dark complexioned Sephardic Jews who had hemolysis and group D relatives of those in group C The hemolysis in group C was due to favism or sensitivity to PAS or sulfonamides

Osmotic and mechanical fragility electrophoretic mobility of hemoglobin amino acid content glycolytic activity and catalase activity were normal in all four groups Glutathione was deficient in the red cells of all patients who had a past history of favism or hemolytic anemia due to PAS or

(3) Blood 1 603 612 J ly 1957

sent complement since the latter could be reinstituted by adding fresh AB serum The results suggest an immune mechanism as operating in the pathogenesis of the anemia

► [A pertinent reference is Harris (J Lab & Clin. Med 47 760 1956 1957 58 YEAR BOOK p 246) —Ed.]

**Gene Mutations in Human Hemoglobin Chemical Difference between Normal and Sickle Cell Hemoglobin** V M Ingram (Univ of Cambridge) found that the globins of normal and sickle cell anemia human hemoglobins differ in only 1 of the 300 amino acids present in the 2 proteins One glutamic acid of normal hemoglobin is replaced by valine Chromatograms of the 2 proteins show all peptides to have identical electrophoretic and chromatographic properties except for peptide no 4 This occupies different positions in normal hemoglobin as compared with the hemoglobin of sickle cell anemia indicating that the difference between the 2 proteins is located here

Sickle cell anemia is an inherited molecular disease due to an alteration in the structure of a large protein molecule the globulin portion of the hemoglobin The abnormally low solubility of reduced hemoglobin S which causes the sickling of the erythrocytes in the anemia is presumably a function of the charge distribution on the surface of the molecule The replacement of 2 charged glutamic acid residues for 2 uncharged valines is presumably enough to alter the protein and favor easy crystallization Thus it is now possible to show that a single gene mutation may change one amino acid of the hemoglobin polypeptide chain for the manufacture of which that gene is responsible

**Studies on Destruction of Red Blood Cells** *XII Factors influencing role of S hemoglobin in pathologic physiology of sickle cells anemia and related disorders*—The deoxygenation of blood in sickle cell anemia transforms red cells from biconcave disks into bizarre elongated sickle shaped forms Concomitantly the blood viscosity increases proportionally to the number of red cells altered which accounts for most of the observed abnormalities in this disease and for the greater mechanical fragility of the red cells If blood flow is impeded local hypoxia may increase the extent of sickling increasing the blood viscosity further decreasing blood flow leading to further local hypoxia and thereby establishing a vicious cycle Concentrations of S hemoglobin of at least

(5) Nature 180 3 6 328 Aug 17 1957

positive Coombs test This resembles the drug dependent agglutination of platelets by the serum of a purpura affected patient in the presence of the drug Sedormid[9] Now a positive Coombs test for erythrocytes that appears to be dependent on serum factors plus quinine and acetophenetidin has been encountered

METHOD —For 1 hour 0 1 ml serum 0 1 ml of 2% suspension of erythrocytes and 0 1 ml of a solution of the drug were incubated at 37 C The erythrocytes were washed three times in saline and drained and 0 1 ml antiglobulin serum from rabbits was introduced After the mixture had stood for 15 minutes it was spun for 1 minute shaken gently read grossly and observed microscopically A solid clump without free red blood cells was read as 4+ a few major clumps with intervening red blood cells as 3+ smaller stable clumps as 2+ and scattered fine clumps stable for 5 minutes microscopically as 1+ all other findings were considered negative

CASE 1 —Negro woman 26 showed fulminant hemolysis with a second known contact with quinine Quinine and the patient s fresh serum caused hemolysis in vitro The patient s aged serum was negative but addition of fresh AB serum resulted in a positive Coombs test. Trypsin treatment of the erythrocytes potentiated the Coombs test Inactivation of the fresh AB serum nullified the positive results obtained with the patient s aged serum Thus a drug dependent (quinine) hemolysis and a positive Coombs test were demonstrated and the Coombs test depended in part on factors in the serum which were storage labile and thermolabile

CASE 2 —Negro girl 17 showed hemolytic anemia during intake of acetophenetidin with jaundice dark urine leukocytosis and erythroid hyperplasia of the bone marrow The patient s fresh serum plus compatible red blood cells plus acetophenetidin gave a positive 1+ Coombs test which became stronger when trypsin treated red blood cells were used Fresh AB serum potentiated the phenomenon

Observations with 112 serums from normal persons (fresh serum plus trypsin treated red blood cells plus quinine) showed one direct agglutination two 4+ Coombs four 3+ and twelve 1+ The other 93 were negative In each positive serum the Coombs test was negative when erythrocytes were incubated in the absence of the drug

Indications are increasing that certain drugs affect the immune mechanism inducing thrombocytopenia leukopenia and/or hemolytic anemia The present study identified an erythrocytic agglutinative phenomenon dependent on serum factors and a drug The intake of this drug had caused hemolytic anemia The erythrocytic agglutination depended on stable factors in the patient s serum which resembled incomplete antibodies and labile factors which may repre

oxygen tensions the degree of sickling increased as the pH was lowered

The viscosity at complete deoxygenation was greater for S S than for A S or S C bloods but the viscosity of S A F blood fell within the range of S S bloods The oxygen tension that barely permitted sickling was distinctly greater for S S than for A S bloods The data suggest that the mean corpuscular S hemoglobin concentration (MCSHC) and the degree of change in viscosity on deoxygenation are related phenomena (Fig 57)

Both in solutions and in whole blood irrespective of the total mean corpuscular hemoglobin concentration the first increase in viscosity occurs when the MCSHC is greater than 10 Gm /100 ml In general the MCSHC is related to the clinical manifestations Patients with less than 15 Gm /100 ml were not anemic and had no painful crises those with values between 15 and 18 Gm /100 ml had only mild hemolytic anemia significant anemia bony lesions and painful crises were limited to patients with MCSHC values of more than 20 Gm /100 ml

The increased viscosity of blood when deoxygenated is a major factor in the pathophysiology of S hemoglobinopathies Viscosity changes are greatest at sites of erythroconcentration and are augmented by lowering and diminished by raising the pH of the blood

► [This last is the subject of the next article—Ed ]

*XIII Observations on role of pH in pathogenesis and treatment of painful crisis in sickle cell disease*—Factors that impede blood flow increase the likelihood of sickling in vivo and may increase the blood viscosity thereby further decreasing blood flow increasing the hypoxia and thus increasing the sickling This is the vicious cycle of erythrostasis sickling and viscosity that causes localized ischemia and ultimately thrombosis and infarction Red cells containing high concentrations of S hemoglobin may begin sickling at oxygen tensions commonly present in the body tissues In the asymptomatic sickle cell trait much lower levels of oxygen tension are required to start the sickling

Mortimer S Greenberg and Edward H Kass[7] (Harvard Med School) found that lowering the pH of blood containing S hemoglobin increased the degree of sickling of red cells even if the oxygen tensions were constant At pH 7 5

(7) A M A A h I t. Med 101 355 363 F bru ry 1958

10 12 Gm /100 ml are required for tactoid formation when S hemoglobin is deoxygenated and this tactoid formation is associated with increased viscosity of the hemoglobin solutions

Mortimer S Greenberg Edward H Kass and William B Castle[6] (Harvard Med School) studied 21 Negroes who had various hereditary hemoglobinopathies involving S hemo globin of whom 8 had S S 9 A S, 3 S C and 1 S A F hemo globins The hemoglobins were obtained in solution and the

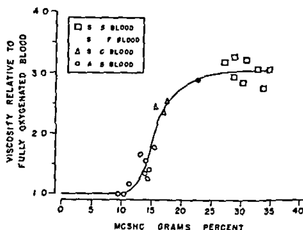



Fig 57 —Relation between mean corpuscular S hemoglobin concentration (MCSHC) and viscosity of fully deoxygenated blood at hematocrit of 35% (Courtesy of Greenberg M S et al J Clin Invest. 36 833 843 June 1957 )

viscosity was determined in an Ostwald viscosimeter after complete oxygenation and complete reduction

The viscosity of reduced A oxygenated A and oxygenated S hemoglobin gradually increased as the concentrations in creased The viscosity of reduced S hemoglobin also in creased at corresponding rates if the concentration was less than 10 Gm /100 ml Above that the viscosity of reduced S hemoglobin rose precipitously At concentrations above 20/100 ml reduced S hemoglobin became a gel At a he matocrit of 25% the viscosity of completely deoxygenated S S blood was approximately that of oxygenated blood at a hematocrit of 50% The pH had no significant effect on the viscosity or degree of sickling in oxygenated blood At lower

(6) J Clin Invest. 36 833 843 J 1957

and $PO_2$ 60 mm Hg few if any cells sickle but more than 90% of the same red cells sickle if the pH is lowered to 7 the PO remaining constant Correspondingly in vivo they found that induced acidosis may precipitate painful crises whereas administration of alkali may be beneficial in treating such crises

Metabolic acidosis was produced on two occasions in a patient with sickle cell anemia by continued administration of ammonium chloride and acetazoleamide The red cells became more susceptible to deoxygenation in vitro there

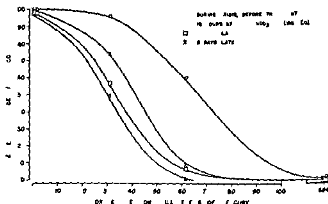



Fig 58—Viscosity changes in blood after administration of alkali to patient with sickle cell anemia undergoing spontaneous painful crisis (Courtesy of Greenberg M S and Kass, K H A M A. Arch Int Med. 101 355 363 February 1958)

was evidence of increased hemolysis more circulating irreversibly sickled forms appeared and typical painful crises occurred

Intravenous sodium bicarbonate 3 3 mEq/kg/hour given to patients with sickle cell disease diminished in vitro sickling of their red cells In 4 of 6 painful crises this dose of sodium bicarbonate resulted in prompt relief from symptoms with changes in blood viscosity (Fig 58) in 2 there was no symptomatic response Two patients were maintained on oral sodium bicarbonate 6 mEq/kg/day for 1 month—the maximum tolerated dose The urine was consistently alkaline Venous pH hemoglobin and viscosity remained unchanged The red cells remained as susceptible to deoxygenation as before therapy

The hazard of metabolic acidosis probably is greatest in

young children but even mild acidosis should be avoided in patients who have the sickle cell trait particularly when the S hemoglobin concentration in red cells is high Management of sickle cell crisis is difficult The prompt relief and associated changes in viscosity after rapidly induced alkalosis suggest that alkalis may help

**Diagnosis of Thalassemia Trait by Starch Block Electrophoresis of Hemoglobin** This trait is a hereditary anemia associated with abnormally shaped erythrocytes and reduced average cell volume It is the heterozygous state for the genetic defect which when homozygous results in severe anemia known as thalassemia major Hemoglobin electrophoresis in a layer of starch prepared from a settled suspension shows that a small fraction of hemoglobin in all normal persons can be separated from the major portion In patients with the thalassemia trait the amount of this fraction is significantly increased above normal Park S Gerald (Children s Med Center Boston) and Louis K Diamond[8] (Harvard Univ ) performed this test in 25 unrelated adults all parents of children with thalassemia major

Normal adult hemoglobin patterns at pH 8 6 show three components (1) a major component known as $A_1$ (2) a fast minor component migrating to the anode just in advance of $A_1$ and producing the characteristic pointed shape of the zone electrophoretic pattern and (3) the slow minor component known as A with mobility comparable to hemoglobin E This A component is the portion characteristically increased in thalassemia trait An elevated A level is a necessary criterion for diagnosis of thalassemia trait Several hundred blood specimens of children and adults with assorted hematologic and other diseases were studied In every instance in which the $A_2$ content was elevated presumptive diagnosis of thalassemia trait on clinical grounds could be made Reduced mean cell (erythrocyte) volume was likewise found in each

If it is assumed that typical childhood thalassemia major represents the homozygous state for the thalassemia gene then the parents must be heterozygous for thalassemia Since microcytosis and increased $A_2$ fraction were constant in each parent they are suggested as minimal diagnostic criteria for the thalassemia trait

(8) Blood 13 61 69 J y 1958

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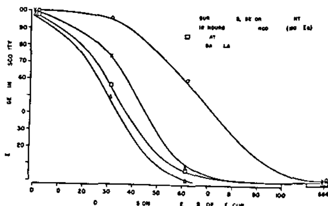


Fig 58 —Viscosity changes blood ft adm st t on f alkal to pat e t w th kle cell nemi u derg g po t neous pa f l s (C rt y f C berg M S a d Ka s K H A M A A ch Int Med. 101 355 363 F b y 1958)

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(8) Blood 13 61 69 J y 1958

The degree of elevation of the $A_2$ fraction was discontinuous but appeared to be identical in affected members of single pedigrees Thus the discontinuity appeared to be genetically controlled The $A_2$ content in some adults with the thalassemia trait was only slightly elevated but sufficed to separate them from normal persons ✓

► [The detection of a minor protein abnormality may indeed be the only way in which a minor phenotypic abnormality can be recognized as for example with deficiency of antihemophilic globulin in the female carrier of hemophilia (see p 333) —Ed ]

**Hemolytic Anemia in Adults and Mediastinal Tumors** Intrathoracic Medullary Heterotopias according to A Paraf G Decroix and J Caroli[9], have never before been recognized during life

Woman 71 entered the hospital in 1956 She had been treated regularly by liver extracts and later by vitamin $B_{12}$ since 1944 when Biermer s anemia was diagnosed Rounded mediastinal masses were shown by x rays at the right and left bases of the thorax (Fig 59) The masses were posterior paravertebral and continuous with the costovertebral plane The right mass had been recognized for 13 years and the left for 7 years and successive x rays had demonstrated a slow increase in size

Exploratory puncture of the right intrathoracic mass revealed erythroblastosis and a hemolytic process was confirmed by reticulocytosis (7%) considerable erythroblastosis both in marrow and in trathoracic mass increase of osmotic fragility and increased excretion of urobilinogen Splenomegaly had been known for 26 years the half life of the erythrocytes was short—16 days Radiobiologic studies proved the noxious role of the spleen making possible the diagnosis of heterotopic medullary paravertebral formations—apparently the first time this diagnosis had been made in vivo

The authors found 3 heterotopic medullary intrathoracic masses at autopsy in an old man with spherocytic hemolytic anemia Analysis of this case and others from the literature was made In 4 cases there was familial spherocytic hemolytic anemia The hemolytic anemia in the case described here without spherocytosis and familial history is perhaps similar to the types described by Crosby although his cases were familial In 2 cases the type of hemolytic anemia was unknown Medullary ectopic masses have also been reported in generalized arteriosclerosis without mention of splenomegaly and in pyloric cancer with hepatic and lymph node metastases

The time of appearance of heterotopic medullary formations in hemolytic disease is variable They were observed

(9) Sema e hop Par s 33 493 502 Dec. 0 1957

at ages 59 75 81 and 70 but also at 50 and 28 In all but 1 case in which masses were found in the sacral region they were situated in the posterior thoracic region along the vertebral column (5th 10th dorsal) under the parietal *pleura at the costovertebral angle In all but 1 instance the* masses had capsules which isolated them completely from the vertebrae They were dark red raspberry or chestnut



F g 59 —Left l t l w J ly 1956 (C urt y f P f A t l S m n h p P n 33 493 50 D 20 1957)

red and resembled the color of splenic pulp Generally (5 cases) there were 2 masses 1 right and 1 left often 1 was larger than the other Sometimes the formations were numerous varying from hazelnut to fist sized

Smears from the masses resembled those of bone marrow with marked erythroblastic hyperplasia and considerable cellular density Other cellular lines—myeloid and megakaryocytes—were well represented Reticular cells surcharged with ferric pigment and fatty cells were also seen Histologic sections revealed a reticulum identifying these masses with normal hemopoietic medullary tissue but abnormally localized

Generally extramedullary hemopoietic foci disappear at birth but connective tissue conserves throughout life the power of forming blood cells which may be revealed in certain pathologic conditions such as leukemias or hyper hemolysis Thus chronic medullary stimulation due to hy perdestruction of erythrocytes causes erythroblastosis of the bone marrow and may result in the appearance of heterotopic medullary foci

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## REGULATION OF ERYTHROPOIESIS

► This heading is used in a limited sense with reference to numerous articles principally concerned with the detection definition and source of an erythropoietic substance present in the plasma of animals and man under conditions of anemic or hypoxic anoxia of the arterial blood. The variations in methodology are numerous as are the areas of present dis agreement among workers Critical reading of the originals is essential for a complete picture of the present state of this subject—Ed

**Effect of Serums from Patients with Anoxia on Prolif erative Activity of Human Erythropoietic Tissue in Vitro** Hypoxia influences the homeostasis of erythropoiesis but not apparently by a direct effect on the marrow Thus plasma or plasma fractions from animals made anoxic have produced variable results when injected into normal ani mals not universally interpreted as evidence for increased erythropoiesis Y Matoth Naomi Biezunski and G Szabo[1] (Hebrew Univ Jerusalem) used an in vitro tissue culture technic Normal human bone marrow cell suspensions (pref erably group O) were incubated in homologous plasma clots in presence of normal serum and serums from patients with various forms of anoxia and the number of erythroid cells capable of mitosis (early and intermediate normo blasts) were quantitated Differences in numbers after incu bation represented the cell proliferation during incubation

The number of early and intermediate normoblasts after 17 hours incubation in normal serum about equaled the number before incubation indicating that cell proliferation balanced the number of cells lost The serums of 16 patients with anoxia—4 with polycythemia secondary to cyanotic congenital heart disease and 12 with anemia of varying eti ology—were incubated in this system Increases of 130

(1) J Lab. & Clin M d. 51 4 0-4 8 M h 1958

180% in the number of early and intermediate normoblasts were induced with 7 serums and of over 180% with 6 With the serums of the other 3 patients with anemia whose hemo globin levels were above 5 Gm /100 ml the erythroid cells did not increase significantly compared with the effect of normal serum The data strongly suggest that a humoral anoxic factor stimulates erythropoiesis and that the degree of anoxia whether of anoxic or anemic type is correlated with the degree of stimulation

► [The authors overestimate the difficulties of peripheral blood studies in animals and underestimate the problems of marrow incubation and ery throid cell counting However the use of human bone marrow for the detection of human erythropoietic factor as well as the small quantity of test serum required offers definite advantages —Ed.]

Presence of Plasma Erythropoietin in Hypoxic Rats with or without Kidney(s) and/or Spleen Hypoxic hypoxia in rats is known to stimulate production of an erythropoietic factor as do bleeding and cobalt administration Jacobson recently reported that bleeding and cobalt chloride admin istration did not produce circulating erythropoietin in the absence of the kidneys and postulated that the kidney is the site of production of the erythropoietic factor However E A Mirand and T C Prentice[2] (Roswell Park Mem l Inst Buffalo) demonstrated that hypoxic hypoxia rats with or without their kidneys or spleen *can* produce erythropoi etin

Rats were placed in chambers aerated with mixtures of nitrogen and approximately 10% oxygen for 4-120 hours Some were nephrectomized and/or splenectomized with minimal blood loss At the end of the particular exposure period the rats were killed and plasma was obtained and injected intravenously into recipient hypophysectomized rats on 2 successive days On day 3 approximately 1 μc Fe [9] was given intravenously and on day 4 a 24-hour Fe [9] up take was done

The Fe [9] uptake indicated that erythropietic factor was elevated in the plasma of hypoxic rats during a limited time 4-24 hours In contrast animals made anemic from bleeding or administration of phenylhydrazine show persistently elevated erythropoietic factor in their plasma as long as they have a significant degree of anemia Erythropoietin was produced in the absence of the kidneys and/or spleen in

(2) P oc Soc. Exp B l & Med 96 49 51 O tobe 1957

rats subjected to hypoxic hypoxia Hence neither the kidney nor the spleen is the production site of erythropoietin under hypoxic hypoxia

It is unknown whether there are different erythropoietins and different production sites If but one kind of erythropoietin is produced the results suggest that the kidney and spleen are not the production sites

► [Similarly Erslev (A M A Arch. Int Med. 101 407 1958) could not detect differences in the level of erythropoietic factor in bled uremic rabbits 20 hours after nephrectomy or ureteral ligation that is whether the kidneys had been removed or were present after ureteral ligation However after 72 hours erythropoietic factor was decreased in both groups of animals —Ed ]

**Influence of Transfusions on Erythropoietic Stimulating Factor (ESF) of Anemic Patients** The ESF factor has been demonstrated in the blood of anemic animals and of some patients with certain blood dyscrasias Paul T Medici Albert S Gordon Sam J Piliero A Leonard Luhby and Perihan Yuceoglu[3] assayed the plasma of 3 children with Cooley s anemia and 1 child with chronic hypoplastic anemia for the amount of such a factor before and after transfusions The plasma was injected into rats and the ESF estimated by the increases in red cells hemoglobin hematocrit and reticulocytes as well as the percentages of marrow erythroid cells

Boiled plasma filtrates obtained from these patients just before they received transfusion when hemoglobin levels ranged from 4 5 to 6 Gm /100 ml displayed strong erythropoietic stimulating activity Transfusion to high hemoglobin levels with whole blood whole blood and packed cells or only packed cells caused lowering in the activity of this factor in most cases to levels which were not detectable

The finding of considerable amounts of ESF in the plasma of the child with chronic aregenerative anemia disagrees with a previous observation on this patient when similarly anemic Experimental work has documented fluctuations in the quantity of ESF produced though the animals remained anemic

Transfusions given patients with Cooley s anemia resulted in the virtual disappearance of the ESF from the plasma The transfused cells apparently reduced the hypoxia and sharply curtailed production of the factor which is fairly rapidly utilized or excreted

(3) Acta ha mat. 18 325 336 N mbe 1957

► [As in animal experiments these clinical observations indicate that the anemia and not some other aspect of the patient s illness was responsible for the increased ESF —Ed ]

**Studies on Nature of Plasma Erythropoietic Factor(s)** The chemical nature of the factor is unknown but some of its physical attributes have been described It is stable over a wide temperature range acid soluble destructible by ashing and not precipitable by perchloric acid The active factor is not removed by passage through either positive or negative ion exchange resin columns James W Linman Frank H Bethell and Martha J Long[4] found such a factor extractable with ether from boiled plasma extracts of anemic rabbits The residues were inactive

When given to the normal rat this factor produced erythrocytosis due to microcytes reticulocytosis and myeloid erythrocytic hyperplasia without increasing the hemoglobin or hematocrit values or iron incorporation values Ether extracts of whole unmodified plasma from anemic rats evoked an identical response in the recipient

Current data indicate more than one plasma factor One just defined is heat stable ether soluble and probably a lipid It stimulates erythroblastic division but not hemoglobin synthesis Another studied by several other workers as well is relatively thermolabile insoluble in ether and probably protein or mucoprotein in nature It appears to augment hemoglobin production The apparent discrepancies in the results obtained by various investigators may be due to the presence of two plasma erythropoietic factors which differ in nature and mode of action

The presence of stimulatory activity in the material extracted twice with ether with evaporation to dryness between extractions and the absence of such activity in the other fractions obtained in this procedure indicates that the factor is ether soluble Boiling and precipitation with perchloric acid do not alter the factor as measured by the response in the normal rat

Erythropoietic stimulatory activity has been demonstrated in plasma serum milk yellow bone marrow and urine but not in other organs or tissues The commonest experimental methods to stimulate production of the factor are repeated bleedings administration of phenylhydrazine or simulated high altitude Cobalt and anemia secondary to

(4) J Lab & Cl n M d 51 8 16 J y 1958

total body x irradiation have also enhanced the donors plasma erythropoietic activity In man erythropoietic stimulatory activity has been demonstrated in the plasma of patients with polycythemia vera and secondary polycythemia, anemias of varied etiology after venous obstruction to a limb and in umbilical cord blood

The sites of production of the erythropoietic factors are unknown but they are apparently not formed in hemopoietic or other radiation sensitive tissue Recent studies have implicated the kidney as a possible locus of formation [but see the article by Mirand and Prentice p 257—Ed ]

► [It seems paradoxical that an erythropoietic factor should not increase the hemoglobin level Indeed the hematologic phenomena ascribed to the ether soluble factor sound remarkably like those of a hemolytic agent with an effect on red cells like serum lysolecithin Its source might be the well known increase in serum lipid after blood loss —Ed ]

**Humoral Regulation of Erythropoiesis IV Relative Heat Stability of Erythropoietin** Frederick Stohlman Jr and George Brecher[5] (Nat l Inst of Health) showed that erythropoiesis could be stimulated in the sublethally irradiated or hypophysectomized rat by injection of a threefold concentrated acidified boiled extract of plasma from rats exposed to simulated altitude or from rabbits with phenylhydrazine induced anemia Fe [59] incorporation was the significant determination in the recipients There was no relation between activity and coexisting liver disease in phenylhydrazine treated animals

Heating acidified plasma at 100 C for 10 minutes destroyed 70 90% of the erythropoietic activity Further heating does not further decrease the activity Thus the reaction is nonlinear The kinetics of the reaction are probably complex The assay technic is too insensitive to detect differences of a few per cent which might occur at the end of a simple exponential curve or a higher-order reaction

Other investigators have also detected erythropoietic activity in concentrated boiled plasma extracts Inability of others to demonstrate activity in some lots of anemic plasma human or animal may be due to the destruction of much of the material before testing rather than to lack of the stimulating factor

The small fraction of residual activity present after prolonged boiling does not warrant the designation of eryth

(5) Proc. Soc Exper B 1 & Med 95 797 800 A & S '4. 1957

ropoietin as a heat stable material A separate heat stable component cannot be assumed to be present though this possibility has not been excluded

**Concentration of Highly Potent Erythropoietic Activity from Urine of Anemic Patients** Donald C Van Dyke Joseph F Garcia and John H Lawrence[6] (Univ of California) screened many patients with various hematologic disorders for plasma erythropoietic titer using the $Fe^{59}$ incorporation in red cells of rats as an assay Some patients with aplastic anemia showed a marked elevation in their titer and from the urine of some a highly potent erythropoietin was extracted

One ml of untreated plasma from normal persons consistently gave an average $Fe^{59}$ incorporation of 26% in the red cells of hypophysectomized rats compared with 6% for control rats given injections of saline Erythropoietic titer was not elevated above normal in any of the patients assayed except 3 children with aplastic anemia In these 1 ml plasma produced a 40 50% incorporation of $Fe^{59}$ in 16 hours In 2 of the 3 children the erythropoietic activity of 1 ml urine was as high as that of 1 ml plasma whereas normal urine shows no activity The third patient s urine was inactive When 1 ml active urine was injected daily the average hematocrit and red cell volume were significantly increased and a definite polycythemia was produced in the rats No such change followed the injection of urine from a normal person

When a concentrate of the active urine prepared by ultra *filtration* was injected at a dose equivalent to 50 ml daily for 14 days into normal adult rats a polycythemia was produced which exceeded that resulting from exposure to a simulated altitude of 15 000 ft for the same period The high potency of such urine has allowed its assay in normal rats

Thus certain patients classified as having aplastic anemia produce and excrete erythropoietic substance in excessive quantities In some the mechanism responsible for this high rate of production and excretion may be analogous to that responsible for the high level of follicle stimulating hormone in the castrate or menopausal woman in that production of the stimulant is uncontrolled because the target

(6) P Soc E p B l & M d 96 541 544 Nov mb r 1957

organ fails to respond and there is no regulatory feedback mechanism

The source of production of the erythropoietic material has not been investigated Presumably that found in the *urine originates from plasma*

**Erythropoietic Activity in Plasma of Patients with Polycythemia Vera and Secondary Polycythemia** was studied by A N Contopoulos Rollin McCombs John H Lawrence and Miriam E Simpson[7] (Univ of California) by injecting the plasma into hypophysectomized rats Of 12 animals given plasma from patients with polycythemia vera 9 showed a statistically significant increase in the total red cell volume or total hemoglobin Rats receiving plasma from patients with the polycythemia of stress or from normal subjects showed no such response $Fe^{59}$ uptake was increased in the blood of those rats which responded thus confirming the conclusion that erythropoiesis was stimulated

This study provides further evidence that patients with polycythemia vera have an erythropoietic stimulant in their blood The lack of *response to plasma from normal* donors and patients with polycythemia of stress indicates that this humoral erythropoietic stimulant is present in low concentrations under normal conditions of erythropoiesis and increased under conditions of increased red cell production The stimulant is heat stable and possibly protein free A humoral erythropoietic stimulant has been reported in animals subjected to hypoxia or hemorrhage or given phenylhydrazine but its relation to the stimulant circulating in patients with polycythemia vera is unknown

The site of production of the erythropoietic stimulating factor is unknown The pituitary contains a factor which can correct the anemia seen after hypophysectomy and can produce polycythemia in the normal or hypophysectomized rat The kidney also is the site of production of an erythropoietic factor

► [These observations confirm those of others such as Linman Bethell and Tascott (1957 58 YEAR BOOK p 279) —Ed ]

(7) Blood 12 614 618 July 1957

# PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

**Studies on Biochemical Defect of Pernicious Anemia I In Vitro Observations on Oxygen Consumption Heme Synthesis and Deoxyribonucleic Acid Synthesis by Pernicious Anemia Bone Marrow** In microbiologic systems folic acid and vitamin $B_1$ are important in synthesis of purines pyrimidines methyl groups and possibly deoxyribose Similar processes may be involved in patients with pernicious anemia

To precisely interpret the effects on bone marrow E Donnall Thomas and Harry L Lochte Jr[8] (Columbia Univ ) studied oxygen consumption heme synthesis as measured by the rate of incorporation of $C^{14}$ glycine into heme and deoxyribonucleic acid (DNA) synthesis by measuring the rate of incorporation of $C^{14}$ formate into thymine Bone marrow was aspirated from patients with classic pernicious anemia in relapse and dispersed through wire screens Aliquots were pipetted into incubation vessels The specimens were then incubated with normal serum serum from patients with pernicious anemia and pernicious anemia serum plus 0 1 µg vitamin $B_1$ /ml usually for 5 or 10 hours

Heme synthesis and oxygen consumption were unaffected by normal serum or vitamin $B_1$ but vitamin $B_1$ had direct consistent effect on DNA synthesis The pernicious anemia marrow cells differed considerably in response to 0 2 µg / ml of folic acid In 2 experiments (table) the marrow of 1 patient responded to folic acid but the other did not whereas the combination of vitamin $B_{12}$ and folic acid induced a response that roughly was the sum of the individual effects alone This may indicate that the two substances are not related in their mode of action

These short term experiments showed that vitamin $B_{12}$ affects DNA synthesis but not oxygen consumption or heme synthesis Perhaps longer experiments would show some heme synthesis effects In the first few hours vitamin $B_{12}$ may permit proliferation of cells and later as the cells mature heme synthesis may increase

(8) J Cl I est. 37 166 171 Febru ry 1958

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(7) Blood 12 614 618 July 1957

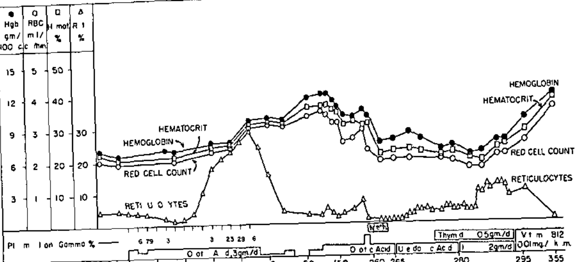



Fig 60 —R p f 54 N g w th p tg t t y pe m t o t a d Eff t of the c mp ds elat d t 1 c d th w t d ed wh el p e occ rr d ft 5 m th of th py (C t y f Ru dles R W a d B w S S J Bl d 13 99 114 F b u y 1958 )

EFFECT OF VITAMIN $B_{12}$ (01 μG/ML) FOLIC ACID (02 μG/ML) AND BOTH VITAMINS ON DEOXYRIBONUCLEIC ACID SYNTHESIS BY PERNICIOUS ANEMIA MARROW IN PERNICIOUS ANEMIA SERUM INCUBATED FOR 10 HOURS

| EXPT | SUPPLEMENT | CPM/μM THYMINE |
|---|---|---|
| A | None | 265 |
| | $B_{12}$ | 713 |
| | Folic acid | 1 705 |
| | $B_{12}$ and folic acid | 2 410 |
| B | None | 8 900 |
| | $B_{12}$ | 11 300 |
| | Folic acid | 9 500 |
| | $B_{12}$ and folic acid | 12 690 |

The pernicious anemia marrow cells were shown to be definitely affected by vitamin $B_{12}$ An intrinsic factor is not essential for action of vitamin $B_{12}$ Pernicious anemia serum does not contain an inhibitor of DNA synthesis

► [The conclusions in the last paragraph support observations on megaloblast maturation in specimens of pernicious anemia marrow in vitro by Swan *et al* (Blood 10 735 1955 1956 57 YEAR BOOK p 266) —Ed ]

**Hematologic Responses in Pernicious Anemia to Orotic Acid** This compound first discovered in cow milk whey in 1905 and its chemical structure established in 1930 appears to be a key intermediate in synthesis of pyrimidines Orotic acid has been isolated from the milk of several mammals from yeast liver and dried distiller s solubles and has been found to be an important growth factor in several bacteria and in rats

R Wayne Rundles and Spencer S Brewer Jr[9] (Duke Univ ) administered orotic acid orally 3-6 Gm daily to 11 patients who had pernicious anemia in relapse Partial remission was induced in each which was most striking in 1 patient with postgastrectomy pernicious anemia (Fig 60) The early effects resembled those from small amounts of vitamin $B_{12}$ Reticulocytosis appeared in 7 14 days and was followed by gradual clinical and hematologic improvement None achieved complete remission and some red cell macrocytosis and marrow megaloblastic activity persisted even at the height of improvement Maintenance on orotic acid alone for 5 7 months was inadequate therapy because anemia again increased and the lingual mucosa again atrophied No toxic effects were noted

Orotic acid is an intermediate in synthesis of pyrimidines However, no precursor or derivative of orotic acid was a

(9) Blood 13 99 114 February 1958.

air with constant gentle shaking The supernatant fluid is decanted and the slices are washed 3 times in 10 ml aliquots of buffer HIFC and/or $Co^{60}$ labeled vitamin $B_{12}$ (0 01 µg ) is dissolved in 1 ml of 0 9% NaCl and added before a single incubation Retained radioactivity of the washed slices is determined in a well type scintillation counter

For any given preparation of HIFC optimal concentration produced maximal $Co^{60}$ $B_{12}$ uptake by the liver slices Increasing or decreasing the concentration decreased the uptake of $Co^{60}$ $B_1$ If the liver slices were first incubated in HIFC washed and then incubated with $CO^{60}$ $B_1$ the uptake of radiocobalt was much greater than if incubation was simultaneous With this sequential incubation method the assay of HIFC potency was in close agreement with in vivo assays using the Schilling urinary excretion test in patients with pernicious anemia

When 1 ml aliquots of gastric juice from 4 patients with histamine fast achlorhydria and vitamin $B_1$ deficiency disease were incubated with the rat liver slices that from 2 patients with pernicious anemia had no effect on $Co^{60}$ $B_{12}$ uptake by the liver slices but that from 2 patients with nutritional $B_1$ deficiency and malabsorption syndrome markedly enhanced $Co^{60}$ $B_{12}$ uptake

No in vitro test can be proved to assay intrinsic factor as it has not yet been isolated in pure form However the sequential incubation system accurately predicted the in vivo potency of HIFC p epar t ons and accurately diagnosed $B_1$ deficiency due to lack of intrinsic factor in gastric juice (addisonian pernicious anemia)

► [Together with the work of Miller *et al* the experiments of this author have defined the conditions of an interesting in vitro observation including calcium dependence and Versenate® reversibility which may have specific physiologic implications However hog intrinsic factor is not active as is rat intrinsic factor in the gastrectomized rat in enhancing the uptake of Co B Why then should it work in the rat liver slice? It is thus possible that the present experiments merely indicate another way of measuring the very active thermolabile Co B binding capacity of hog and indeed of rat and human gastric juice. Nevertheless this property is closely related to and may be in common an essential phase of their cl nical intrinsic factor act vity —Ed ]

**Dual Mechanism of Vitamin $B_1$ Plasma Absorption** After massive doses of vitamin $B_1$ significant plasma levels by microbiologic assay can be found early in normal subjects and in patients with pernicious anemia When 0 46-1 µg is given patients show no significant absorption unless intrinsic factor is added Plasma absorption curves using $Co^{60}$ $B_{12}$

active Carbamyl aspartic acid 3 Gm daily produced slight reticulocytosis in 2 patients aspartic acid 15 20 Gm daily with 3 6 Gm orotic acid had little or no effect in 2 others and a concentrate of uridylic and cytidylic acids had some effect in 1 of 2 patients to whom it was given This latter concentrate given to a child with congenital abnormality in pyrimidine biosynthesis who excreted large amounts of orotic acid was remarkably effective

Histidine synthesized by folic acid containing enzymes produced definite hemopoietic stimulus in 2 patients with pernicious anemia Response was quick and suboptimal and did not potentiate that of orotic acid One patient in partial remission from histidine taken for 12 weeks was given folic acid but without additional benefit. Further studies of these and other folic acid metabolites are in progress

Vitamin $B_{12}$ may function differently in nucleoside and nucleic acid synthesis in different biologic systems In bacteria vitamin $B_1$ probably promotes synthesis of methionine nucleosides and/or deoxyribose and possibly activates protein sulfhydryl groups In animals vitamin $B_1$ may promote methyl group neogenesis but probably has nothing to do with transmethylation Vitamin $B_1$ apparently has functions that differ from those of folic acid The degree of remission possible by use of orotic acid suggests that one major consequence of vitamin $B_{12}$ deficiency in man is a defect in pyrimidine biosynthesis and/or incorporation The mechanism by which orotic acid induces partial remission in pernicious anemia is unknown

*Development of Possible in Vitro Assay for Intrinsic Factor* is reported by Victor Herbert[1] (Montefiore Hosp New York) The author s previous experiments have shown that enhancement of $Co^{60}$ $B_{12}$ uptake by hog intrinsic factor concentrate (HIFC) was calcium dependent reversible to an appreciable degree by ethylene diamine tetraacetate (disodium Versenate®) and occurred in the cold as well as at 37 5C Most enhancement by HIFC occurred in the 1st hour of incubation

METHOD—The incubation medium Krebs Ringer solution is maintained at pH 7 5 with 0 1M tris hydroxy amino methane (Tris) buffer with sufficient added CaCl to bring the calcium concentration to 10 mM Rat liver slices 200 300 mg are placed in 20 ml beakers each containing 10 ml buffer incubated 1 hour at 0 C in

(1) Proc Soc E pe B ol & Med. 97 668 671 March 1958

tration and delayed the peak concentration to 12 hours (Fig 61) Though intrinsic factor delayed the appearance of $B_1$ in the plasma it enhanced the hepatic uptake of radioactivity

Control subjects given 200 500 µg $B_1$ showed a slightly diphasic absorption with an early rise in radioactivity a test dose of 10 µg resulted in delayed absorption and 50 100 µg resulted in intermediate absorption curves

It seems likely that the intestine is in some way responsible for the slower rise in radioactivity in the plasma in the presence of intrinsic factor The absorption curves do not conform to those which might be expected if the mechanism were passive diffusion across the intestinal barrier These findings support the concept of a dual mechanism of absorption of vitamin $B_1$ from the gastrointestinal tract Until the mechanisms are better known they should best be referred to as the one mediated by intrinsic factor and the other as absorption independent of intrinsic factor

**Absorption of Vitamin $B_1$ in Control Subjects in Addisonian Pernicious Anemia and in Malabsorption Syndrome** was studied by D L Mollin C C Booth and S J Baker[3] (Postgraduate Med School London) using vitamin $B_1$ labeled with $Co^{56}$ or $Co^{8}$ which have half lives of approximately 72 days The half life of $Co^{60}$ is 5 years which limits the amount that can safely be given

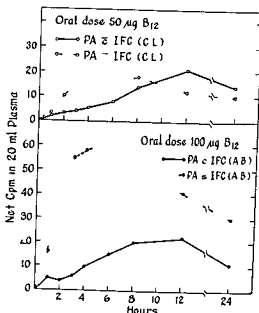
When the labeled vitamin $B_{12}$ was given orally there was an overlap in the amounts absorbed in patients with pernicious anemia compared to control subjects However when the oral dose was accompanied or followed by an injection of 0 25 mg Carbachol (carbamylcholine chloride) the patients with pernicious anemia all absorbed significantly less labeled vitamin than did the normal controls The absorption of $B_{12}$ by all patients with pernicious anemia increased when the oral dose of labeled $B_1$ was given with intrinsic factor concentrate

Of 5 patients with histamine fast achlorhydria 3 absorbed as little $B_{12}$ as did patients with pernicious anemia The amount absorbed increased when Carbachol was injected or intrinsic factor was given In two thirds of the patients with idiopathic steatorrhea most of those with tropical sprue and all with steatorrhea secondary to anatomic lesions of the small intestine $B_1$ absorption was as low as in patients with

(3) B t J H m t 3 412-4 8 O t b 1957

were obtained by Alfred Doscherholmen and Paul S Hagen[2] (Univ of Minnesota) in patients with pernicious anemia with or without added intrinsic factor and in normal subjects The oral test doses of cyanocobalamin to which adequate but safe tracer amounts of $Co^{60}$ $B_{12}$ were added ranged from 0 56 to 500 µg

With test doses of 0 56 µg $B_{12}$ without intrinsic factor




F g 61 —C mpar son of pl ma d cti ty 2 pat e t w th p rn o s emia after o al admin st t n of 50 and 100 µg d t ve v tam B w th d w th t nt c fa tor co cent te (IFC) (C rte y f D herh lm A and H g P S J Cl In est. 36 1551 1557 N emb 1957 )

negligible or no plasma absorption (radioactivity) was detected When intrinsic factor was added absorption curves were obtained which were similar to those in control subjects characterized by plasma radioactivity appearing after 4 hours with a peak concentration at 8 hours

Oral doses of 50 300 µg without intrinsic factor given to patients with pernicious anemia were followed by absorption curves characterized by an early rise in plasma radioactivity and peak concentrations 4 6 hours later Addition of intrinsic factor abolished the early rise in plasma concen

(2) J Cl n In t. 36 1551 1557 N mb 195

tomic lesions of the small intestine and some who had tropical sprue Antibiotics were of no help in those who had idiopathic steatorrhea but $B_{12}$ absorption improved in some when given a gluten free diet

**Absorption and Excretion of Vitamin $B_1$ in Subjects Infected with Diphyllobothrium Latum and in Noninfected Subjects Following Oral Administration of Radioactive $B_{12}$** Wolmar Nyberg[4] (Univ of Helsingfors) studied absorption of radioactive $B_1$ in carriers of D latum with and without anemia and in normal subjects When oral $B_{12}$ is given to carriers of D latum a large proportion is absorbed by the parasite which thus competes with the host for the available $B_{12}$ in the intestine and typical $B_1$ deficiency may develop

In patients with anemia the fish tapeworm absorbed from 75 100% of oral doses ranging between 1 and 2 µg and some of the remainder of the dose appeared in the feces With higher oral doses percentage of uptake by the tapeworm decreased and uptake by the host increased whereas total excretion in the feces and the percentage excreted increased Absorption and excretion were greater in normal subjects In patients with fish tapeworm but without anemia absorption of 0 34 2 68 µg doses was within the range regarded as the normal daily requirement but on an average was 55% less than that absorbed by normal subjects which is a highly significant variation In these patients the radioactivity of expelled tapeworms was about 180% higher than the radioactivity in the feces

The position of the tapeworm in the proximal intestine allows it to absorb larger amounts of $B_{12}$ than if it were situated distally The tapeworm precipitates anemia by absorbing such large amounts that none or little is left for the host The length of the tapeworm has little effect Infection with D latum always affects the host s capacity to absorb ingested vitamin $B_1$

► [Obviously if as is often the case there is decreased secretion of gastric intrinsic factor the worm has a further advantage in its competition with the patient.—Ed.]

**Effect of Indole Compounds on Vitamin $B_1$ Utilization** A definite relation has never been established between indole metabolism and megaloblastic anemias though a hemolytic *like anemia with many features of pernicious anemia has*

(4) Acta haemat. 19 90 98 February 1958

pernicious anemia However none of these patients increased their absorption when the vitamin was given with 50 mg intrinsic factor In 20 patients who absorbed subnormal amounts (Fig 62) a course of antibiotic therapy increased the absorption to normal in 4 patients with diverticulosis of the small intestine in 2 of 4 with intestinal short circuits associated with Crohn s disease in 2 of 3 other patients with an intestinal short circuit or blind loop and in 3

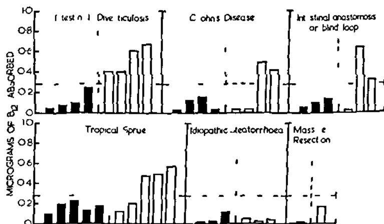



Fig 62—Effect of antibiotic on absorption of radioactive vitamin $B_{12}$ by 20 patients with malabsorption syndrome Each received 1 μg radioactive $B_{12}$ usually plus 50 mg intrinsic factor before and after course of antibiotic Black columns denote amount of $B_{12}$ absorbed before course of antibiotic Open columns denote amount absorbed after antibiotic (Courtesy of Mollin D L et al Brit J Haemat. 3 412 428 October 1957)

of 5 with chronic tropical sprue Absorption did not improve in 3 patients with idiopathic steatorrhea or in 1 who had massive resection of the small intestine

Some control patients with free acid in gastric juice absorb only small amounts of oral vitamin $B_{12}$ These can be differentiated from patients with pernicious anemia because their absorption of $B_{12}$ increases when they are given an injection of Carbachol This does not occur in patients with pernicious anemia Absorption of oral $B_{12}$ increases to a normal range in patients with pernicious anemia when the vitamin is given with oral intrinsic factor

In patients with the malabsorption syndrome who were unable to absorb $B_{12}$ normally intrinsic factor was of no benefit but a course of antibiotic therapy effectively increased the amount of $B_{12}$ absorbed by most who d ana

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Effect of Indole Compounds on Vitamin $B_{12}$ Utilization A definite relation has never been established between indole metabolism and megaloblastic anemias though a hemolytic like anemia with many features of pernicious anemia has

(4) Acta h m t. 19 90-98 F bru ry 1958

been produced in dogs on vitamin B deficient diets by oral feeding of pure indole Jerry Drexler[5] (Cleveland Clinic) studied the effect of indole compounds on utilization of $B_1$ by a mutant strain of Escherichia coli which is dependent on vitamin $B_1$ for growth

Several indole compounds prevented use of $B_{12}$ by the micro organism and the inhibition could be reversed by adding $B_{12}$ Other E coli micro organisms not dependent on $B_1$ were unaffected by the indole compounds The mechanism by which indole compounds bind the vitamin is unknown

Unsaturated indoles such as indole acrylic acid inhibit the growth of E coli but this can be reversed by tryptophan Tryptophan had no effect in the present study A vitamin $B_1$ indole complex could not be demonstrated Since inhibition of $B_{12}$ utilization was reversed by excess $B_1$ the indole compound apparently competitively inhibits some enzymatic system necessary for utilization of vitamin $B_{12}$

Macrocytic anemia associated with intestinal strictures and anastomoses has been attributed to change in bacterial flora of the small intestine which interferes with formation or utilization of hemopoietic material Coliform micro-organisms produce indole and indoles inhibit use of vitamin $B_1$ an essential hemopoietic material Thus an indole product of gastrointestinal micro-organisms could conceivably be the toxic factor in megaloblastic anemia of intestinal blind loops Antibiotics prevent formation of indoles and development of anemia The anemia produced in dogs by indole feeding is likely due to interference with vitamin $B_{12}$ utilization

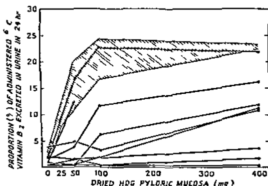
► [This interesting observation deserves further study

Recently in our opinion the pharmaceutical industry has turned the clock backward by its attempts to redevelop practical methods of oral therapy for pernicious anemia employing combinations of vitamin B and hog gastric intrinsic factor Physicians who recall the enormous therapeutic advance that followed the advent of parenteral therapy in the thirties will probably agree On the other hand the discovery of vitamin B and much of the modern scientific knowledge concerning both vitamin B and the gastric intrinsic factor are to be credited to the work of the scientists within the pharmaceutical industry With the discovery of vitamin B in the late forties the problem of the occasional species pecific sensitivity to injectable liver extracts was eliminated by the use of injection of vitamin B and a guarantee of the efficacy of all parenteral preparations by laboratory assay methods became possible The following 3 articles document

(5) Blood 13 239 244 Ma h 1958

some of the difficulties inherent in any method of oral therapy in pernicious anemia —Ed.]

**Reduced Effect of Heterologous Intrinsic Factor after Prolonged Oral Treatment in Pernicious Anemia.** Oral vitamin $B_{12}$ plus hog intrinsic factor is a rational treatment of per nicious anemia However a good initial response has been followed by a decrease in hemoglobin and red cells after a period of treatment *Michael Schwartz Per Lous and Einar* Meulengracht[6] (Copenhagen) observed this phenomenon in several patients during the past 2 years Occasionally the




F g 63 —U y t on S h ll g t st pe f rm d with d ff t m ts f hog pyl ic m cosa in 9 p t ent w th perni mia lly treated ½-4 yea H t h d ea ep se t lue for 4 eated p t ent (Court y f S hw rtz M et l La et 1 751 753 Ap 13 1957 )

blood status may be improved by increasing the dosage but usually oral treatment must be supplemented by injections

When tested by the Schilling test (urinary excretion of orally ingested vitamin $B_1$ labeled with radioactive cobalt) untreated patients with pernicious anemia excrete more ra dioactive material in the urine when the dose of hog intrinsic factor is increased This indicates increased intestinal ab sorption Beyond a certain limit *further increases in the* amount of intrinsic factor have only slight effects on the absorption of vitamin $B_1$ Patients treated by injection for more than 3 years showed the same response as untreated patients

However 9 patients who were treated by oral intrinsic factor plus vitamin $B_1$ for 6 months to 4 years did not show this uniform response (Fig 63) Seven absorbed much less

(6) La t 1 751 753 Ap 13 1957

vitamin $B_1$ though the dose of hog intrinsic factor was the same Similar results were obtained with highly purified intrinsic factor also made of hog pyloric mucosa When human intrinsic factor was administered the intestinal absorption of vitamin $B_{12}$ was the same in patients who had previously received oral commercial hog intrinsic factor injections of vitamin $B_{12}$ or who were untreated

All commercially available intrinsic factor is made of hog pyloric mucosa Patients with untreated pernicious anemia absorb considerably more vitamin $B_{12}$ if given small amounts of these preparations However after treatment for some time this absorption is apparently blocked Its cause is not known but the block is not present when homologous (human) intrinsic factor is administered This block is presumably the cause of failure in some cases of oral treatment with vitamin $B_{12}$ plus intrinsic factor

► [It has been suggested that the development of resistance is the result of impurities in the crude hog intrinsic factor preparations and highly purified hog intrinsic factor preparations have been reported not to produce progressive refractoriness In any case a reduced effectiveness of hog intrinsic factor will not be proved until such has been shown to occur in individual patients successively titrated over some months with respect to a standard initially submaximal dose of a pool of human gastric juice. —Ed ]

**Maintenance Therapy in Pernicious Anemia Controlled by Determining Vitamin $B_{12}$ Level in Plasma** Combinations of pure vitamin plus intrinsic factor have been used in oral treatment of pernicious anemia but the adequacy of such therapy is disputed Since low serum levels of the vitamin may precede clinical signs of deficiency such determinations should not only be specific for but also provide the earliest detection of inadequate therapy H P Ostergaard Kristensen Jesper Lund A Søeborg Ohlsen and Jørgen Pedersen[7] (Copenhagen) followed the serum levels of vitamin $B_1$ and the hematologic status in 12 patients with pernicious anemia treated with oral medications

Before treatment the plasma levels averaged 57 μμg/ml ranging from 10 to 120 The lower limit of normal is 150 μμg/ml The hemoglobin averaged 49% and red cells 1 740 000/cu mm Ten patients were started with intramuscular vitamin $B_1$ usually 30 60 μg daily for 10 days 1 was given liver extract and 1 was given oral vitamin $B_{12}$ plus intrinsic factor from the start After initial therapy of

(7) Lancet 1 1266 1270 Ju 2 1957

10-31 days treatment of 9 of the 10 patients was changed to maintenance with oral vitamin plus intrinsic factor

The levels of vitamin $B_{12}$ in the plasma (Fig 64) were all low during oral treatment The patient with the lowest curve (Case 1) had received no injections In 8 of the 9 who had received injections the plasma levels had become normal before oral therapy was instituted and during the succeeding months on oral therapy the levels again reached abnormally

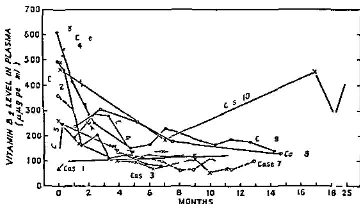



Fig 64—V tamin B lev l n plasm f 10 pat ents w th pern anemia i m inte an w th t min B nd h g pylori mu osa All but Case 1 w initially t eated by inject ons f y tall e itamin B (300 1 080 µg) wh h had ra sed tamin B l l n pla ma to mal. (Courtesy f Krist en H P O et al Lancet 1 1 66-1270 June 22 1957)

low levels Only 1 patient (Case 10) had an entirely normal level of plasma vitamin $B_{12}$ after more than 2 years of oral therapy Of 7 patients who had repeat sternal marrow aspiration findings were abnormal in 6

These results show that the oral administration of a commercially available mixture of vitamin $B_{12}$ and intrinsic factor did not keep the bone marrow and serum level of vitamin within normal limits though the amount of hemoglobin and the erythrocyte counts remained normal Patients on maintenance therapy for pernicious anemia can have a low serum level of vitamin for months without clinical signs of deficiency Therefore determinations of serum or plasma levels are necessary if the efficacy of maintenance therapy is to be properly assessed

Low levels in the plasma indicate depleted tissue reserves

In patients so affected the risk of hematologic relapse or development of neurologic defect is high Until more reliable methods are available for determining the efficacy of treatment parenteral treatment seems to be the method of choice for maintenance in doses of 100 μg every 2 weeks

Maintenance Therapy of Pernicious Anemia with Oral Administration of Intrinsic Factor and Vitamin $B_1$ Louis Lowenstein Lauder Brunton Lorne Shapiro Nannie de Leeuw and Maurice Dufresne[8] (Montreal) followed 36 patients who had pernicious anemia treated with oral vitamin $B_{12}$ for 3 years

Therapy consisted of capsules containing 5 μg vitamin $B_{12}$ and 50 mg defatted desiccated hog pyloric mucosa One fourth of the patients received 1 capsule every 3 days one fourth 1 capsule daily one fourth 2 capsules daily and the rest 3 capsules daily Most had previously been treated with 30 60 μg vitamin $B_1$ parenterally every 2-4 weeks After 3 years of oral maintenance therapy the patients were re evaluated clinically hematologically by determination of the serum levels of vitamin $B_{12}$ and by repeated Schilling tests

During treatment no patient had clinical or neurologic relapse Four acquired mild to moderate anemia Bone marrow relapses occurred in 19 of the 36 patients and of these 14 were on relatively low doses The serum levels of vitamin $B_{12}$ (Fig 65) arranged in the 4 groups according to the amount of oral medication taken were almost all less than 200 μμg /ml with no definite trend related to the amount taken orally

Though an initial hematologic response resulted from as little as 1 capsule every 3 days an apparently refractory state often developed later during which increased doses of oral therapy produced either no remission or partial and unsatisfactory remission and failed to elevate the serum levels of vitamin $B_{1}$

After termination of oral therapy Schilling tests were done in 15 patients first with radioactive vitamin $B_{12}$ ($Co^{58}$ $B_1$ ) alone and then with the radioactive vitamin plus hog pyloric mucosa With the former urinary excretion was 0-4 3% repeated with hog pyloric mucosa 0 24 9% When the tests were performed in patients not previously treated

(8) Canad M A J 77 923 930 Nov 15 1957

F g 65—S rum vit min $B_{12}$ c trati ft 3 y m te a th apy (C t y f Low t in L t l C d M A J 77 923 930 N 15 1957)

with oral therapy the same batch of radioactive vitamin $B_{12}$ plus hog pyloric mucosa resulted in excretion of over 15% of the ingested radioactivity These results indicate that the previous oral therapy had produced a functional state of vari

able refractoriness to the heterologous source of intrinsic factor Others have shown that administration of normal human gastric juice as a substitute for hog pyloric mucosa results in normal absorption of radioactive vitamin $B_{12}$ in patients treated with the vitamin plus hog pyloric mucosa These patients had apparently become refractory to such therapy

Oral administration of small amounts of vitamin $B_{12}$ with desiccated hog pyloric mucosa as a source of intrinsic factor is not satisfactory maintenance therapy in addisonian pernicious anemia

Response of Megaloblastic Anemia to Prednisolone has been documented in 8 patients by A Doig R H Girdwood J J R Duthie and J D E Knox[9] (Edinburgh) Each patient was observed for spontaneous hematologic remission for a short period before therapy was begun Each was then given 10 mg prednisolone 3 times daily orally for 3 weeks All remained in hospital for at least a week after prednisolone was stopped and were eventually treated with vitamin $B_1$ or folic acid

Four patients had addisonian pernicious anemia 2 had celiac disease persisting into adult life with megaloblastic anemia which did not respond to cyanocobalamin and 2 had rheumatoid arthritis with unusual forms of megaloblastic anemia In the latter patients the serum cyanocobalamin level was persistently low despite normal absorption of labeled cyanocobalamin In a ninth patient megaloblastic anemia developed surprisingly rapidly after partial gastrectomy All of these patients responded hematologically to prednisolone except the fourth who was treated for only 6 days

Prednisolone is not recommended as treatment for any type of megaloblastic anemia In general the red cell count and hemoglobin level rose more slowly the reticulocyte response was suboptimal and the initial fall of serum iron always present in the first 48 hours of successful $B_{12}$ or folic acid therapy was not observed after prednisolone That prednisolone was effective in both folic acid and $B_{12}$ deficiency indicates that its effect was not due to intrinsic factor activity Absorption of radioactive $B_{12}$ was not enhanced

► [A recent study of a similar prednisone induced remission in a single

(9) Lancet 2 966-972 Nov 16 1957

patient with pernicious anemia by Frost and Goldwein (New England J Med 258 1096 May 29 1958) showed an enhanced uptake of Co B but no increase of intrinsic factor secretion By analogy with the beneficial action of adrenal steroids on intractable sprue an effect on intestinal absorption seems probable in some patients —Ed.]

Macrocytic Anemia of Pregnancy is rare but when present is an important cause of maternal morbidity It is more frequent among poorer persons in tropical countries and where nutrition is deficient Onset is usually insidious most commonly in the last trimester A E R Buckle and Sidney Shaw[1] (London) report 5 cases

Gastric secretion is depressed during pregnancy but no deficiency in intrinsic factor has been demonstrated and liver injections are not beneficial Diets are not always deficient in patients who acquire macrocytic anemia of pregnancy and diet alone cannot explain the disease No abnormality in serum levels of vitamin $B_1$ has been demonstrated Apparently fat absorption is normal in most patients with this anemia

Macrocytic anemia of pregnancy may occur at any age in the childbearing period Symptoms often acute are those secondary to anemia though a few patients also have gastrointestinal upsets sore tongue jaundice and splenomegaly Many patients are asymptomatic and the diagnosis is made after routine hematologic investigation

The anemia is frequently refractory to injections of liver extract though it may respond to whole liver or crude extracts given orally Vitamin $B_1$ and folic acid are equally effective in over all evaluations though some patients will respond to one and not the other

The diagnosis is made by peripheral blood smear Findings are typically macrocytes and possibly megaloblasts in the peripheral blood Some cases may masquerade as iron deficiency anemia because of microcytosis or hypochromia of the red cells The possibility of macrocytic anemia should be considered in any case of severe anemia in pregnancy Marrow aspiration should be done before treatment is started A megaloblastic marrow confirms the diagnosis Gastric analysis should be done to determine the presence of acid

If anemia is present at the first prenatal visit iron and ascorbic acid are prescribed Hemoglobin estimation is repeated at week 32 or 36 and if the anemia has not responded

(1) J Obst & Gynec Brit Emp 64 396-404 J 1957

the foregoing investigations are carried out Although the deficiency is commonly of folic acid some patients respond well to vitamin $B_1$ Treatment may be with either agent depending on the response

► [Few modern observers appreciate that the megaloblastic anemia of pregnancy may be due to different deficiencies These include folic acid, perhaps sometimes combined with ascorbic acid deficiency and less commonly vitamin B deficiency as well (Lowenstein *et al* Am J Obst. & Gynec. 70 1309 1955 1956 57 YEAR BOOK p 268) With good reason the term megaloblastic rather than macrocytic has been applied to the anemia of these pregnant patients because of the frequency of microcytosis and hypochromia of the red cells Such patients as those in the authors Cases 1 and 2 do not masquerade as iron deficiency they have it in fact. Now in the presence of a deficiency of both folic acid and iron the marrow cannot respond to the *latter until it* has begun to respond to the former That is acceleration of hemoglobin production can take place only when restoration of function of the earlier stages of erythropoiesis dependent on folic acid has taken place The failure of preliminary iron therapy in 2 of the authors patients does not mean that iron deficiency was also present —Ed ]

**Megaloblastic Anemia Associated with Pregnancy or Puerperium Report of Three Cases with Normal Serum Vitamin $B_1$ Levels and Subsequent Response to Treatment with** *Vitamin $B_{12}$* is presented by Andreas Killander[2] (Univ of Uppsala) The cause of this form of megaloblastic anemia remains obscure It is not definitely related to diet secretion of the intrinsic factor or to fat absorption In the past reports of vitamin $B_{12}$ therapy have been conflicting

Normal men and women have serum vitamin $B_{12}$ levels of 150 1 200 μμg /ml 100 150 is considered borderline and less than 100 μμg /ml is definitely subnormal

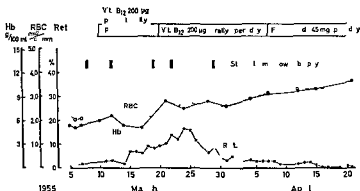
Woman 31 quadripara had been tired and had ulcers of the mouth for 2 months after the third delivery Sore mouth recurred a month after the last delivery Five months later she was pale and tired and had a smooth red tongue with ulcers of the mucous membrane Blood study revealed 6 6 Gm hemoglobin/100 ml 1 800 000 red cells 3 600 white cells and 1 4% reticulocytes Normoblasts and megaloblasts were found in the bone marrow Gastric aspiration contained free hydrochloric acid No ova were found in the feces Serum iron was normal and serum vitamin $B_1$ was 130 μμg /ml borderline normal

*Parenteral and* oral therapy with 200 μg vitamin $B_1$ daily resulted in protracted reticulocytosis (Fig 66) Normoblastic erythropoiesis did not appear until the 19th day Folic acid produced no further effect. She had received 2 000 μg of parenteral $B_{12}$ during 10 days followed by 3 600 μg orally during the next 18 days When last seen 10 months after therapy had been stopped remission had been sustained

Symptoms signs and therapeutic response are diverse in pernicious anemia associated with pregnancy or the puerpe

(2) Acta haemat. 19 9 19 Jan ry 1958

rium The response to vitamin $B_{12}$ is surprising in view of the normal or borderline serum levels present Response differs from that in classic addisonian pernicious anemia in that reticulocyte and bone marrow responses are slow and protracted There probably is no actual deficiency of vitamin $B_{12}$ in such patients Spontaneous remission is common Free hydrochloric acid is present in the gastric juice and no proof of dietary deficiency is available It is improbable that




F g 66—M gal bl t m f p erp m in w man 31 (Cou t y f K llan d A A t ha mat 19 9 19 J nuary 1958)

fetal demand would exhaust the mother s stores of vitamin $B_1$ However vitamin $B_1$ may exert its effect by means other than correcting a state of deficiency

Normal serum level of vitamin $B_{12}$ does not exclude therapeutic response to therapy with the vitamin if given in massive doses in these particular patients

► [Rarely patients with megaloblastic anemia during pregnancy have low vitamin B levels Here the level was borderline Nevertheless there is growing recognition that under certain circumstances both vitamin B and folic acid may act pharmacologically rather than merely to abolish a deficiency Large doses of fol c acid may quickly or slowly force serum vitamin B levels down Since normal erythropoiesis in man requires both folic acid and vitamin B large amounts of the latter may here have complemented a moderate deficiency of folic acid.—Ed.]

**Folic Acid Absorption Excretion and Leukocyte Concentration in Tropical Sprue** C E Butterworth Jr Hyman Nadel Enrique Perez Santiago Rafael Santini Jr and Frank H Gardner[3] (Walter Reed Army Inst of Research) gave 5 mg crystalline folic acid orally or intravenously to 8 patients

(3) J Lab & Cl M d. 50 673 681 N mbe 1957

who had tropical sprue and to 5 normal subjects then measured the urinary excretion during the next 5 hours

Whether it was given orally or parenterally, urinary excretion of folic acid was significantly reduced in patients with sprue but the reduction was much greater after the oral test Patients with sprue but in remission excreted normal amounts of folic after the test dose—about 30 times more than the amount which had been excreted before therapy

Only a small percentage of the injected folic acid was detectable in the serum 1 hour after intravenous administration Apparently the plasma clears quickly of folic acid either into the tissues in patients who are depleted and have the syndrome of tropical sprue or into the urine in normal subjects and patients in remission The amount of folic acid present in the leukocytes of patients with untreated sprue is significantly less than in adequately treated patients or normal subjects

Patients with tropical sprue in relapse cannot absorb folic acid adequately and tissue levels are reduced Since folic acid absorption through the intestinal tract improves simultaneously with absorption of other substances the malabsorption of folic acid may be only secondary to intestinal dysfunction Normal persons and patients adequately treated for sprue have similar levels of folic acid in the serum and leukocytes after oral or intravenous doses of folic acid Apparently there is no specific defect in the absorption of folic acid in tropical sprue comparable to the malabsorption of vitamin $B_{12}$ in patients with pernicious anemia Patients with sprue in remission require only the usual amounts of folic acid though they tend to relapse unless the diet is supplemented

No substances were detected in the urine of patients who had sprue which could inhibit the growth of Streptococcus faecalis Since these organisms depend on folic acid for growth it was concluded that no folic acid inhibitors were present in the urine of patients with tropical sprue

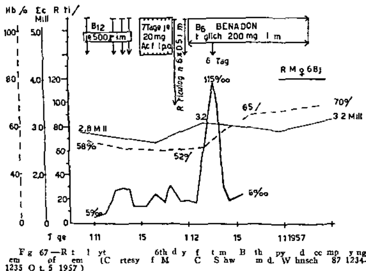
**Megaloblastic Vitamin $B_6$ Deficiency Anemia with Hemochromatosis** C Maier[4] (Zurich) reports a case

Woman 67 was hospitalized for bronchial asthma and cardiac insufficiency She had had acute *pancreatitis with a high urinary diastase* and cholelithias for which cholecystectomy had been performed 17 years previously and 11 years later had been hospitalized for ve

(4) Schweiz med Wchnschr 87 1234-1235 Oct 5 1957

nous thrombosis of the legs and cardiac insufficiency at which time hyperchromic anemia (hemoglobin 66%) had been noted

Examination revealed hyperchromic anemia with 58% (9 Gm /100 ml ) hemoglobin erythrocytes 2 800 000 and color index 1 26 Blood smears showed significant macrocytosis anisocytosis and poikilocytosis average erythrocyte diameter was 9 5 µ There were a few megalocytes Thrombocyte count was 180 000 white cells 10 000 with isolated segmented nuclei lymphocytes 8% eosinophils 0% Sternal puncture showed a macroblastic marrow with numerous large megaloblasts Fasting blood sugar level (Hagedorn) was 156




F g 67—R t l yt 6th d y f t m B th py d cc mp y ng em of em (C rtesy f M C S hw m d. W hnsch 87 1234-1235 O t. 5 1957 )

mg /100 ml Iron tolerance test with 160 mg Fe (ferronicum) by mouth showed the following fasting 228 µg /100 ml after 1 hour 252 µg after 4½ hours 240 µg and after 7 hours 240 µg The Coombs test was negative Excision biopsy of the liver showed insular cirrhosis fatty degeneration and hemosiderosis with pigment in Kupffer liver and inter titial cells Total gastric acidity was 20 free HCl 10 The serum copper level was 85 µg /100 ml No hemochromatosis or abnormal scaling of the skin was noted

Neither vitamin $B_{12}$ nor folic acid was effective in controlling anemia However vitamin $B_6$ (benadon) 200 mg /day produced a maximal reticulocyte crisis on the 6th day followed by remission of anemia (Fig 67)

The patient s striking hematologic response to vitamin $B_6$ (pyridoxine) resembles that of a case reported by Harris *et al* [Proc Soc Exper Biol & Med 91 427 1956 1956 57 YEAR BOOK p 272—Ed ] The diet had been adequate in fact

she was overweight Since there presumably was no deficiency of vitamin $B_6$ in the diet reduced synthesis or absorption in the intestine increased need or abnormal destruction of pyridoxine in intermediate metabolic stages must be considered An interesting question is whether there is a relation between pyridoxine deficiency and hemochromatosis Pyridoxine deficiency in swine is associated with anemia and a high serum iron as *in this patient Among Bantu Negroes*, with whom hemochromatosis is endemic diet is deficient in pyridoxine and niacin and symptoms of pellagra are often present Now that liver cirrhosis in deficiency states has become generally known studies should be made to find whether hemochromatosis with malnutrition rests on a specific pyridoxine deficiency

The morphologic picture in blood and bone marrow in the author s patient agrees exactly with that in 9 patients with megaloblastic anemia and hemochromatosis reported on by Koszewski Three of these who survived long enough were brought to remission with vitamin $B_1$

Hemochromatosis is now attributed by many to a block in intestinal absorption of iron The cause of this mucosal disturbance has been variously attributed to heredity alcohol overeating generally deficient diet and specific pyridoxine deficiency As with other metabolic diseases possibly no single cause but several factors may be responsible for onset of hemochromatosis

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## HYPOCHROMIC ANEMIAS

**Absorption of Hemoglobin Iron** Contrary to previous opinions iron which is present in food in the form of heme compounds can be absorbed Sheila T Callender Barbara J Mallett and Mary D Smith[5] (Univ of Oxford) proved this by feeding hemoglobin labeled with Fe [?] to persons with and without anemia All the subjects absorbed appreciable amounts of the labeled iron

Rabbits were given an intravenous injection of radioactive ferric chloride When the radioactivity of the rabbit blood was about 5 μc /10 ml samples were removed by cardiac

(5) Brit J H mat 3 186-19 1957

puncture the blood lysed with distilled water and fed to human subjects in the fasting state at midmorning The dose given contained 5 mg iron For comparison the same subjects were given 5 mg iron as labeled ferrous sulfate with 1 Gm ascorbic acid The radioactivity derived from the test dose appeared in newly formed red cells

In 11 normal subjects without anemia and with normal serum iron the percentage of oral inorganic iron absorbed was 11-68% with a mean of 25% That absorbed from ingested hemoglobin averaged 10% for raw 7% for cooked hemoglobin In 11 patients with iron deficiency anemia all with low levels of plasma iron the absorption of inorganic iron averaged 58% and of iron from ingested hemoglobin 22% The absorption of iron from hemoglobin is more difficult than the absorption of inorganic iron salts as reflected in the delayed peak of plasma radioactivity in both normal and iron deficient subjects However hemoglobin iron is definitely absorbed

**Comparison of Iron Absorption Test with Determination of Iron Binding Capacity of Serum in Diagnosis of Iron Deficiency** was made by M C Verloop J E Th Meeuwissen and E W M Blokhuis[6] (Univ of Utrecht) Signs and symptoms of iron deficiency may exist while the hemoglobin and serum iron are normal In infections and tumors the serum iron may be decreased without there being any question of generalized iron deficiency Apparently normal men and women showed striking scatter in serum iron levels The latent binding capacity was less than 300 µg /100 ml total binding capacity was less than 415 µg /100 ml and saturation percentage of serum for iron exceeded 25% The absorption rate of orally administered iron was inconstant but was much higher in women than in men

In 30 patients with iron deficiency the fasting level of serum iron was abnormal in all but 2 In each the latent binding capacity was greater than 300 µg /100 ml whereas total binding capacity often was below the normal maximum of 411 µg /100 ml The saturation percentage was lower than 20% in each patient (normally more than 25%) Two hours after administration of 176 mg iron orally the plasma iron was higher than in normal controls and the increase expressed in terms of the fasting level was greater

(6) Brit J H mt. 4 70 81 Jan ry 1958

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(5) Brit J Haemat 3 186-19 1957

complete in 2 Degree of superficial or deep infiltration was not related to severity of anemia Milder degrees of anemia tended to be associated with normal gland concentration Degree of infiltration and atrophy tended to be more severe in older patients Histamine tests showed free acid in 5 of whom 4 showed no atrophy and 1 slight atrophy Among 9 without free acid atrophy was slight in 1 moderate in 3 severe in 3 and complete in 2

After correction of anemia 12 showed no change in amount of infiltration in 6 it was greater and in 1 it was less Degree of atrophy was unchanged in 12 increased in 6 and decreased in 1 Over all results showed the histologic appearance to be unchanged in 9 and worse in 8

The gastric mucosal lesions tended to progress over the year s observation Acid secretion similarly did not improve The epithelial lesions due to iron deficiency tended to im prove The authors conclude that the gastric lesions are not due to iron deficiency but precede the anemia and favor the development of iron deficiency The cause of these abnor malities is unknown

► [On the other hand the next article which documents a clinical im pression of long standing suggests that defective tissue function in the uterus unlike the stomach may be secondary to iron deficiency —Ed ]

**Vicious Circle of Anemia and Menorrhagia** It is usually assumed that as long as blood loss is excessive anemia will persist and the uterus is removed whether or not there is uterine pathology However patients should be classified into those who have obvious uterine abnormality commonly fibroids and those who do not before surgery is advocated Those who have no such pathology may be treated medically

Cecil Harris[8] (St Mary s Hosp Montreal) found that women with menorrhagia and hypochromic anemia may respond to therapy with iron The menstrual loss may im prove as the anemia improves Such patients still should have dilatation and curettage with smears made for cyto logic study All other sources of blood loss especially from the gastrointestinal tract must be excluded since such loss might initiate the entire cycle

Iron deficiency anemia may develop in a patient and insti gate or aggravate menorrhagia A vicious cycle may ensue Proper management is correction of the anemia by effective

(8) C d M A J 77 98 100 J ly 1 19 7

In infections serum iron may fall as low as in iron deficiency but total binding capacity also decreases reducing the latent binding capacity to well below 300 µg /100 ml and the saturation percentage often is less than 25% After 176 mg ferrous iron orally serum iron increased only slightly at 2 hours comparable to rise in normal subjects but much less than in patients with iron deficiency Results in patients with malignancies were comparable

In iron deficiency the iron reserves of the body are the first to be used to maintain erythropoiesis and hypochromic anemia develops only when the iron depots are exhausted At this stage the plasma iron concentration (transport iron) is reduced When ionized iron was given intravenously it disappeared from the plasma and was taken up by the bone marrow more quickly than normal Oral iron was absorbed readily and used for hemoglobin synthesis Two hours after a well performed iron absorption test the rise in serum iron level showed whether or not iron deficiency was present being greater than 250% in iron deficiency The test may fail when absorption is impaired but in sprue and after gastric resection the ferrous chloride was absorbed readily

Determination of the latent binding capacity of serum gives results that are just as convincing as the iron absorption test The former is less troublesome to the patient and can be done without taking a fasting specimen When latent binding capacity exceeds 300 µg /100 ml iron deficiency is likely Determination of the latent iron binding capacity of serum is preferred to the iron absorption test

**Gastric Mucosal Lesions before and after Treatment in Iron Deficiency Anemia** were studied by Fred Lees and F D Rosenthal[7] (Royal Infirm Sheffield) in 21 patients without gastrointestinal bleeding or ulceration Anemia was corrected with iron therapy alone Specimens of gastric mucosa were obtained by suction biopsy tube before treatment and about 1 year later in 19 Whenever possible a qualitative histamine test was performed at biopsy

Of the 19 original specimens 2 were normal Superficial infiltration with lymphocytes plasma cells and occasional polymorphs was mild in 8 moderate in 8 and severe in 1 Deep infiltration was mild in 9 and moderate in 6 There was no atrophy in 8 slight in 3 moderate in 3 severe in 3 and

(7) Q art J M d 27 19 26 Janu ry 1958

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After correction of anemia 12 showed no change in amount of infiltration in 6 it was greater and in 1 it was less Degree of atrophy was unchanged in 12 increased in 6 and decreased in 1 Over all results showed the histologic appearance to be unchanged in 9 and worse in 8

The gastric mucosal lesions tended to progress over the year s observation Acid secretion similarly did not improve The epithelial lesions due to iron deficiency tended to improve The authors conclude that the gastric lesions are not due to iron deficiency but precede the anemia and favor the development of iron deficiency The cause of these abnormalities is unknown

► [On the other hand the next article which documents a clinical impression of long standing suggests that defective tissue function in the uterus unlike the stomach may be secondary to iron deficiency —Ed ]

**Vicious Circle of Anemia and Menorrhagia** It is usually assumed that as long as blood loss is excessive anemia will persist and the uterus is removed whether or not there is uterine pathology However patients should be classified into those who have obvious uterine abnormality commonly fibroids and those who do not before surgery is advocated Those who have no such pathology may be treated medically

Cecil Harris[8] (St Mary s Hosp Montreal) found that women with menorrhagia and hypochromic anemia may respond to therapy with iron The menstrual loss may improve as the anemia improves Such patients still should have dilatation and curettage with smears made for cytologic study All other sources of blood loss especially from the gastrointestinal tract must be excluded since such loss might initiate the *entire cycle*

Iron deficiency anemia may develop in a patient and instigate or aggravate menorrhagia A vicious cycle may ensue Proper management is correction of the anemia by effective

(8) C d. M A J 77 98 100 J ly 1 19 7

therapy with iron not primarily by transfusions and hysterectomy Even if a uterine lesion exists requiring surgery the best preoperative preparation is by iron therapy which will restore blood values [and tissue iron—Ed ] even if there is gross pathology in the uterus Prolonged hospitalization may be obviated by treating the anemia before admission Transfusions are unnecessary and the preoperative and most likely the postoperative period will be shortened

CASE 1 —Woman 37 was in heart failure Menses had been normal until a few months before admission shortly after the appearance of symptoms of anemia Menstrual loss then became heavy The hemoglobin was 3 3 Gm /100 ml hematocrit 12% and mean corpuscular hemoglobin concentration 27% Ferrous calcium citrate was given orally A reticulocyte response was noted and clinical and hematologic improvement followed Hemoglobin reached 15 2 Gm /100 ml and hematocrit 48% Menstruation immediately returned to normal and subsequent gynecologic examinations were normal

CASE 2 —Woman 40 had hypochromic anemia associated with menorrhagia especially for the preceding 3 years Curettage on two occasions was normal Three other hematinics had been ineffective but ferrous calcium citrate given orally produced the desired response After 10 weeks the hemoglobin level reached 13 6 Gm /100 ml and menstrual loss diminished to the levels which had been present before the preceding 3 years

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## OTHER ANEMIAS

**Effect of Inflammation on Utilization of Erythrocyte and Transferrin Bound Radioiron for Red Cell Production** Infection and inflammation impair the ability of bone marrow to respond to increased demands for red cell production Emil J Freireich Aaron Miller Charles P Emerson and Joseph F Ross[9] (Boston Univ ) demonstrated that in dogs in the presence of inflammation the rate of reuse of $Fe^{59}$ from senescent red cells is markedly impaired whereas the use of plasma transferrin bound iron is not impaired The result is hypoferremia and impaired hemoglobin production

Some animals were made iron heavy by repeated intravenous injections of Feojectin® Others were made iron deficient by repeated bleedings Senescent nonviable $Fe^{59}$ labeled cells were prepared in another dog and transferrin bound $Fe^{59}$ made by incubating $Fe^{59}$ in the plasma of still

(9) Blood 12 972 983 November 1957

another Sterile inflammations were produced by injecting turpentine subcutaneously

The infected animals showed distinct impairment of reuse of Fe from senescent red cells *The control animal used 3 4 times more Fe* [9] for red cell production than did the abscessed animal Yet when plasma transferrin bound iron was injected the rate of incorporation of Fe [9] was similar *in the abscessed and normal animals The reuse of iron from* senescent red cells was most impaired during active inflammation These findings were repeatedly demonstrated whether the animals were iron deficient had normal iron stores or *were iron heavy*

The findings indicate that inflammation causes a delay in the release of iron from senescent red cells to the plasma transferrin iron pool Inflammation does not impair bone marrow use of plasma transferrin iron for red cell production The diminished reuse of Fe [9] from senescent red cells probably is not due to deficient red cell breakdown or hemoglobin catabolism since injection of *large quantities of iron* in other chemical forms is similarly affected by inflammation

Since the results were the same regardless of the original iron content of the animal the relative tissue requirement for iron in the abscessed animals was probably not a factor The results could be explained by a defect in the release of iron from destroyed red cells to the plasma transferrin pool coupled with the unimpaired removal of iron from the plasma transferrin pool by the hemopoietic tissues for red cell production

*This* impaired reuse of *hemoglobin* iron *results* in an inadequate supply of iron for red cell production and is important in the genesis of secondary anemias of chronic infection malignancy uremia and cirrhosis in which hypoferremia *is present Large quantities of parenteral iron do not* increase the amount of iron available for red cell production since most of the injected iron is deposited in the tissues and the hypoferremia is corrected for only short periods

► [However e pecially because the red cells of patients with chronic infections are not usually hypochromic it would be a mistake to assume that iron deviation is the only causative factor —Ed ]

**Survival Time of Erythrocyte in Myxedema and Hyperthyroidism** Normal survival time is 120±15 days In many *clinical states associated with anemia the basal metabolic* rate is increased and the survival time of the erythrocytes

decreased Jason E McClellan Charles Donegan Oscar A Thorup and Byrd S Leavell[1] (Univ of Virginia) studied erythrocyte survival in myxedema and hyperthyroidism using the Ashby and radioactive chromium technics

Red cells from 4 patients with myxedema which were transfused into normal recipients survived a normal period in each instance Survival time was also normal when erythrocytes from a normal donor were transfused into a mildly anemic patient with myxedema Erythrocytes from 3 patients with hyperthyroidism survived normally when transfused into normal recipients In 2 patients with marked hy

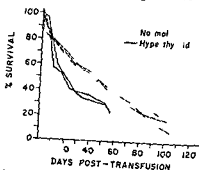



Fig 68 —S rvi al t m of yth ocyt n 3 rm l pe ns nd 2 p t nts w th hyperthyr d m d term ed by ch om m t h (Cou t sy f McClella J E, et al J Lab & Cl n Med 51 91 96 Jan y 1958)

perthyroidism the 50% survival time of autogenous red cells was about 18 days but when transfused into 3 normal persons it was 39 48 days (Fig 68)

The results indicate that hyperhemolysis is not a factor in the anemia of myxedema which is likely due to decreased erythropoiesis However the finding of a shortened survival time of red cells in some patients with hyperthyroidism agrees with the reports of other investigators of increased fecal urobilinogen excretion in hyperthyroidism and evidence of increased erythropoiesis by bone marrow aspiration The normal survival of cells when transfused into normal persons suggests an environmental factor is responsible Its nature is unknown

**Characterization of Anemia Associated with Chronic Renal Insufficiency** This anemia is thought to be due to a combination of erythroid depression and in some instances a hemolytic mechanism The most important factor is the de

(1) J Lab & Cl n Med. 51 91 96 January 1958

pression of erythropoiesis In a few cases blood loss from the gastrointestinal tract and/or an increased rate of red cell destruction are contributing factors J Philip Loge Robert D Lange and Carl V Moore (Washington Univ) studied 26 anemic patients aged 18 71 with chronic renal insufficiency and azotemia Twelve had chronic glomerulonephritis 11 hypertensive cardiovascular disease with nephrosclerosis 1 hypertensive cardiovascular disease and chronic pyelonephritis 1 arteriolar nephrosclerosis with acute pyelonephritis and 1 polycystic disease of the kidneys

The anemia was uniformly normochromic and usually normocytic In 3 patients the mean corpuscular volume was consistently above 100 cu μ in none was it less than 81 cu μ Serum iron was 58 125 μg/100 ml Utilization of radioactive iron was determined 8 times in 7 patients and *was significantly decreased in each compared to normal* controls which was interpreted as probably representing depressed erythropoiesis There was no evidence of increased destruction of red cells in 5 measurements in 4 patients

Some patients became rapidly anemic in the absence of detectable bleeding Slight to moderate reticulocytosis was found in all 26 Patients cells transfused into normal persons showed a normal survival rate in each even when the cells were being rapidly destroyed in the patient clearly demonstrating the extracorpuscular nature of the hemolytic process Several patients showed increased hemolysis of normal *red cells which were transfused into them* The Coombs test was negative in all patients

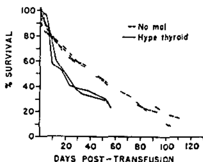
Tests of osmotic fragility indicated beginning hemolysis above 0 48% saline in only 3 patients in each an extracorpuscular hemolytic factor had been demonstrated Mechanical fragility in vitro was normal in 7 patients tested Serum bilirubin was normal in all 26 Fecal urobilinogen determined in 5 was normal in each Two had significant gastrointestinal loss of blood

Invariably in uremia erythropoiesis is depressed Occasionally the anemia becomes rapidly progressive although no blood loss is detectable At these times there is increased breakdown of red cells Thus at times the anemia must be due to a combination of depressed erythropoiesis and increased red cell destruction

(2) Am. J M d 24 4 18 J y 1958

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F g 68—S rv al t me f ythrocyt s n 3 no m l pe and 2 p t e t with hyperthy d m d t m ed by h m m tech (C te y of M Cl ll n J E t l J Lab & Cl n M d 51 91 96 J ua y 1958)

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( ) Am. J Med. 24 4 18 J y 1958

**Burr Red Cell and Azotemia** This cell is a poikilocyte measuring about 7 5 μ or less with one or more large spiny projections along its periphery (Fig 69) It has been described in patients with azotemia gastric carcinoma bleeding peptic ulcer and in some cases of hemolytic anemia W A Aherne[3] (Radcliffe Infirm Oxford England) found them most commonly in progressive and ultimately fatal renal failure not related to any particular cause of this failure The burr poikilocyte is not always a harbinger of death but



Fig 69—Tr g l a d e nt c bu p k l cyte r d d fr m ×1000 (C t sy f Ab rn W A J Cl P th 10 252 257 Aug t 195 )

may also occur in reversible renal failure Of 25 patients with azotemia 13 had burr cells in the peripheral blood and only 1 of these had blood urea levels less than 150 mg/100 ml In general the burr poikilocyte may not be expected in significant numbers until the blood urea is 175 200 mg/100 ml usually in those cases in which the blood urea has risen steadily over a number of days

In the past the anemia of progressive renal failure has been explained as marrow depression by some retained toxic metabolites [and still is usually according to the preceding article—Ed ] However the bone marrow is usually hyperplastic and mild to moderate reticulocytosis is present These observations plus reticuloendothelial hemosiderosis and the frequent finding of erythrophagocytosis suggest a hemolytic rather than a dyshemopoietic anemia Perhaps the burr cell of uremia represents abnormality in the enzyme systems which maintain the normal red cell structure

(3) J Clin. Path 10 252 57 Aug t 1957

The anemia may be due to the phagocytic removal of these cells in the reticuloendothelial system A cell similar to the burr poikilocyte apparently of different origin may occur in a treatable acute hemloytic anemia of childhood The anemia of renal failure may in some cases be due to the sequestration and breakdown of deformed inert burr poikilocytes

**Aplastic Anemia Clinical Analysis of 50 Patients** seen at the University of Virginia Hospitals between 1933 and 1956 is presented by Daniel N Mohler Harry R Yates *Walter R Stern and Byrd S Leavell*[4] *Age at onset was 4 82* the average being 43 46% were over 50 Only 2 were Negroes Ratio of men to women was 35 15 In 7 toxic exposure was thought to be the cause (in 3 to benzol and in 1 each to phenylbutazone Mesantoin chloramphenicol and arsenic) Though 9 had a family history of anemia in only 2—brothers with Fanconi s syndrome—was this documented aplastic anemia

In 24% the skin was pigmented grayish brown and 5 others had scattered cafe au lait spots Purpura or petechiae were present in 48% all of whom had thrombocytopenia Retinal hemorrhages were present in 36% significant lymphadenopathy in 24% splenomegaly in 34% and hepatomegaly in 32% Testicular atrophy was present in 24% of the men

Peripheral blood showed pancytopenia in 37 patients anemia alone in 7 anemia and leukopenia in 4 and anemia and thrombocytopenia in 2 The anemia was macrocytic in 32 normocytic in 10 and microcytic in none In 43 per cent of lymphocytes was increased (relative lymphocytosis in 37 and absolute *increase in 6) Reticulocyte counts were over 5% in* 11 patients 2 5% in 10 and under 2% in the others Only 9 had consistent reticulocyte counts of 0 1% or under Among 14 patients tested fecal urobilinogen was elevated in 8 they *were considered to have a hemolytic element but the main* defect was decreased blood production

Bone marrow aspiration showed 37 to be hypocellular but 3 of these later became hypercellular and 3 normocellular *In 8 cellularity of the bone marrow was originally normal* but 2 of these showed erythroid hypoplasia and 3 later became hypocellular Of 5 presenting with hypercellular bone marrow 1 later became hypocellular

*Among the 35 who died survival was 5 weeks to 20 years*

(4) \ g M M th 85 134 137 M h 1958

after diagnosis Among the 15 who were still living duration of illness varied from 21 months to 18 years Prognosis was most favorable in patients with anemia alone and worst in those with pancytopenia Six patients had complete remission with return of blood to normal 4 after corticosteroid therapy 1 after splenectomy and 1 spontaneously In 6 others remission was partial or temporary The largest number of deaths was due to infection Hemorrhage was the commonest cause in those with thrombocytopenia

The most effective treatment is withdrawal of the offending toxic agent if it can be determined In idiopathic types transfusions corticosteroids and splenectomy are basic therapies Vitamin $B_{12}$ and folic acid are ineffective and iron therapy is not only useless but increases danger of exogenous hemochromatosis

**Treatment of Refractory Anemia or Bone Marrow Failure** is usually discouraging Painstaking care however makes the patient more comfortable often prolongs productive life for months or years and occasionally a remission occurs The subject is reviewed by Carl V Moore[5] (*Washington Univ*)

All marrow elements may be involved or only one or two cell types The anemia is usually refractory to available therapy The marrow may be hypoplastic normally cellular hypercellular or partially fibrotic The peripheral pancytopenia may be due to maturation arrest in the marrow failure to deliver cells to the peripheral blood or peripheral destruction of cells manufactured at normal or greater than normal rates

Refractory anemia may be idiopathic or may follow exposure to chemical agents and ionizing radiation Rarely it is congenital The spleen is not directly involved but treatment with transfusions leads to transfusion hemosiderosis splenomegaly and aggravation of the anemia due to increased destruction of red cells The diseases most likely to be confused with hypoplastic anemia are subleukemic leukemia and other myelophthisic anemias Differentiation depends on bone marrow examination

A few patients whose exposure to a chemical or ionizing radiation is known may improve if further exposure is avoided In most patients it is difficult to be sure that a chemical has actually caused the aplasia Patients should be ad

(5) J Chron c D s 6 324 331 Octobe 1957

vised against the use of hair dyes insecticides plant sprays volatile solvents and all drugs except those specifically pre scribed Prognosis is definitely better when exposure to a toxin can be identified and eliminated though the mortality rate remains high About 15 cases of benign thymoma and refractory anemia have now been described and 4 improved markedly after thymectomy

The main treatment of refractory anemia is by transfu sions Blood typing of patient and donors should include Rh factor and whatever other minor factors the laboratory can identify The transfusion should be as type specific as pos sible All cross matches should be checked with an indirect Coombs test on the donor s red cells and patient s plasma Blood should be transfused within the first 5 days of collec tion in acid citrate dextrose solution Transfusions should be given only when the hemoglobin has dropped below 9 Gm /100 ml unless they are given to treat shock due to hemorrhage Despite all precautions after 50 or more trans fusions the frequency of reactions gradually increases Some perhaps most result from acquired sensitivity to transfused leukocytes and platelets and can be prevented by removing the buffy coat before the blood is given [See ar ticle by Brittingham and Chaplin page 227—Ed ]

Other supportive measures include an adequate diet but excessively high protein large amounts of liver or similar special diets are of no further value Death usually occurs from infection or hemorrhage not as a rule from anemia Prophylactic use of broad spectrum antibiotics is unsatis factory and hazardous Correct antibiotics should be started as soon as an infection develops The mouth should be kept clean dental work limited to that required catheterizations avoided and constipation prevented Hemorrhagic manifes tations almost invariably are due to thrombocytopenia Cor ticoid therapy increases capillary resistance though the platelet count is unaltered Prednisone may be started as 5 mg every 6 hours increased if necessary and then decreased until the minimum effective level is attained If hemorrhagic manifestations are not controlled by 50 mg /day larger doses are seldom beneficial If bleeding is severe platelet transfusions may be tried All medications should if possible

be given orally since injections cause hematomas and abscesses may form

Attempts to stimulate marrow function are usually ineffective though the occasional response to ACTH other corticoids or cobalt makes it worth while to try such therapy Splenectomy is valuable if the spleen is enlarged and destroying cells at an accelerated rate or if it is depressing marrow function The authors have evidence of the latter in only 2 patients If transfusions are required more often than every 10 days an increased rate of hemolysis can be assumed Hemolysis can be directly measured by labeling the patient s own red cells with $Cr^{51}$ and determining the half time survival If radioactivity over the spleen is several times greater than over the liver the spleen may be at least partially responsible for the increased hemolysis Splenectomy should be done only in patients with demonstrable hemolysis in which the spleen is actively participating It should not be done indiscriminately

► [This and the preceding article provide authoritative discussions of the topic of refractory anemia and its management —Ed ]

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## POLYCYTHEMIAS

**Erythrocytosis Associated with Cerebellar Hemangioblastoma** A case is reported by Bernard Blumberg and Ralph M Myerson[6] (V A Hosp Philadelphia)

Man 40 had headache diplopia and ataxia for 3 months Examination revealed papilledema and bilateral cerebellar signs The red blood cell count was 4 700 000 and the white cell count 20 000 A ventriculogram revealed internal hydrocephalus and craniotomy disclosed a telangiectatic cyst in the midline cerebellar fossa No tissue was removed On re exploration of the posterior fossa 2 years later tumor tissue was found protruding through the dura The lesion was inoperable At that time the hemoglobin was over *20 Gm /100 ml* the red cell count ranged as high as 9 600 000 and the hematocrit up to 82% Platelet and white cell counts were low A biopsy specimen was interpreted as hemangioblastoma Bone marrow study revealed erythroid hyperplasia The reticulocyte count was 1 4% Phlebotomies and radioactive phosphorus decreased the erythrocytosis but not to normal levels

Cerebellar hemangioblastomas or angioreticulomas are rare Less than 20% are associated with erythrocytosis and

(6) Ne [illegible] 367 369 M [illegible] 1957

this has been noted only with the solid type of tumor Im provement has occurred in some reported cases after re moval of the tumor The present case supports the view that the blood changes are those of erythrocytosis rather than polycythemia vera The bone marrow showed hyperplasia only of the erythroid elements The relatively normal arterial oxygen saturations at rest and after exercise plus the normal pulmonary function studies in this case are strong evidence that the erythrocytosis is not secondary to anoxia

The pathogenesis of the erythrocytosis is still unex plained Several theories concern the relationship between erythrocytosis and cerebellar hemangioblastoma One pos tulates injury to or pressure on a specific erythropoietic center in the diencephalon The injection of silicaceous earth into the diencephalon of rabbits has produced polycythemia Depression of the respiratory center by pressure of the slowly growing tumor leading to a respiratory rate of 10/minute arterial oxygen saturation of 84% and polycy themia has been reported A third theory proposes the for mation of erythroid elements by the tumor itself but the erythroid hyperplasia of the marrow noted in the present case and in others suggests that the marrow is the site of in creased erythropoiesis Finally it has been postulated that some cerebellar hemangioblastomas elaborate a substance capable of stimulating erythropoiesis

**Polycythemia Associated with Benign Kidney Lesion Report of Case of Erythrocytosis with Hydronephrosis with Remission of Polycythemia Following Nephrectomy** is presented by William M Cooper and William B Tuttle[7] (Univ of Pittsburgh) This is the first such case reported Nine cases have been reported of polycythemia associated with hypernephroma in 3 of which remissions followed nephrectomy

Man 55 florid and slightly obese had progressive fatigability weakness anorexia daily headaches and lightheadedness At age 8 he had had Bright s disease lasting 2 years Blood pressure was 150/100 mm Hg Examination revealed a large left upper quadrant abdominal mass Urine specimens consistently contained protein and white and red blood cells The nonprotein nitrogen level was 41 mg / 100 ml Phenolsulfonphthalein excretion was 28% in 30 minutes and 49% in 4 hours The blood cell counts are listed in the table

Pyelograms showed a functionless left kidney and considerable cal cification Nephrectomy was performed two hydronephrotic sacs

(7) A I t M d. 47 1008-1015 Nov mbe 1957

were removed The pathologic diagnosis was severe left hydronephrosis *secondary to ureteropelvic obstruction by renal calculus* Recovery was uneventful Blood pressure and serial blood counts became normal (table)

The cause of polycythemia associated with renal disease is obscure Experimental studies have suggested that erythrogenic humoral factors are present implicating the kidney as one source

SERIAL BLOOD CELL COUNTS AND HEMATOCRIT DETERMINATIONS

| DATE | RED BLOOD CELL COUNT PER CU MM | HEMOGLOBIN | HEMATOCRIT | WHITE BLOOD CELL COUNT PER CU MM | PLATELETS |
|---|---|---|---|---|---|
| 4 13 50 | 6 380 000 | 17 5 | | 11 300 | |
| 4 26 50 | 9 850 000 | 19 0 | 68 | 8 000 | 308 000 |
| 5 9 50 | 8 290 000 | 18 5 | | 6 400 | 360 000 |
| 5 15 50 | 7 200 000 | 19 0 | 68 | 7 000 | |
| FOUR VENESECTIONS TOTALING 2200 CC FROM 5 20 50 TO 5 31 50 | | | | | |
| 6 5 50 | 5 240 000 | 16 0 | 50 | 7 500 | |
| 6 29 50 | 5 490 000 | 18 0 | | 9 000 | 302 000 |
| NEPHRECTOMY 7 3 50 | | | | | |
| 7 19 50 | 4 020 000 | 15 0 | 47 | 9 600 | |
| 9 21 50 | 4 290 000 | 13 5 | 41 | 9 200 | 230 000 |
| 7 2 51 | 4 840 000 | 13 5 | 46 | 11 300 | 248 000 |
| 3 9 55 | 4 740 000 | 14 5 | 46 | 10 100 | 318 000 |
| 4 25 56 | 4 280 000 | 13 0 | 44 | 8 500 | 260 000 |

► [Because both *renal tumor* and *rarely hydronephrosis* (as in this case) have been associated with polycythemia a common basis in renal vascular stasis or ischemia might be inferred Stefanini has recently produced polycythemia experimentally by constriction of renal veins —Ed ]—

**Treatment of Polycythemia Vera** is reviewed by Edward H Reinhard and Betty Hahneman[8] (Washington Univ ) This is a chronic disease of unknown etiology with clinical manifestations of headaches fatigability dizziness *pruritus splenomegaly plethora cyanosis and systolic hypertension* Hemoglobin hematocrit and erythrocyte levels are increased consistently and in most cases also the leukocyte and thrombocyte concentrations Most of the clinical manifestations and the most serious complication of polycythemia vera *intravascular thrombosis are due to three factors increased total blood volume increased viscosity* and thrombocytosis

Until the etiology of the disease is known the aim of

(8) J Chron c D s. 6 332 346, Octobe 1957

therapy must be to relieve symptoms minimize the danger of intravascular thrombosis and avoid if possible procedures which might increase the incidence of leukemia leukemoid reactions and myelofibrosis

Total blood volume can be lowered and blood viscosity decreased by removing blood by hemolysis by suppressing the bone marrow or by inducing an iron deficiency state Venesection is the quickest method of removing blood and this should be followed by some form of therapy to suppress the marrow In young patients with minimal or no vascular disease and in patients with mild polycythemia with a hematocrit less than 60% and no thrombocytosis it may be worth while to try to control the disease by phlebotomies alone removing 500 1 000 cc blood every 3-4 months The disadvantages of venesection alone are that it does not affect the leukocyte and platelet levels control of the erythrocyte level is uneven it is unpleasant for the patient and an iron deficiency with hypochromia of the erythrocytes invariably is induced which may cause significant symptoms

Phenylhydrazine hemolyzes red blood cells In large doses it may cause jaundice and severe anemia If this drug is used the blood volume should be lowered by phlebotomies first and phenylhydrazine given in small interrupted courses 0 1 Gm daily or every other day for 10 doses repeated at intervals of 10 days as often as necessary to maintain control Therapeutic doses have not been reported to cause liver damage This therapy is probably most useful in patients who no longer respond to safe doses of $P^{3}$ and whose veins have thrombosed Iron deficient diets have the disadvantage that iron has important functions in the body other than in erythropoiesis (it is present in myoglobin cytochrome catalase and peroxidase) and if iron is sufficiently deficient to control the polycythemia the patient usually feels tired

Use of the earliest chemotherapeutic agents to suppress the marrow benzol and Fowler s solution is no longer justified since their toxic effects may be formidable Nitrogen mustard produces inconsistent therapeutic effects of brief duration necessitating frequent unpleasant retreatment Newer derivatives of nitrogen mustard such as triethylene melamine have had inadequate clinical trials

Radiation therapy is successful in suppressing the marrow especially when total body spray radiation is used by

an experienced radiologist Radioactive phosphorus therapy has certain advantages over x ray treatment The effects of radiation therapy of any type may be delayed several weeks or months Radioactive phosphorus is easy to administer is free from immediate toxicity relieves symptoms has a smoother effect on hematologic control and prolongs the duration of remissions

The authors present practice is to treat all patients with polycythemia who are under age 40 and all with mild cases at any age with phlebotomies alone for as long as the dis ease can be controlled by one or two of 500 cc each no more often than every 3 4 months If phlebotomy is needed more often or the cells become markedly hypochromic $P^{32}$ is started The hematocrit is first reduced to 55% by phleboto mies and then a single intravenous injection of 4 5 mc $P^{32}$ is given No calculation is necessary according to body weight Complete blood counts are obtained each month and more phlebotomies are performed if the hematocrit rises above 55% No further $P^{32}$ is given at least for 3 months when another 1 4 mc is given if the hematocrit is significantly above 45% or the platelet count is still high After another 3 months a third injection of 1 2 mc $P^{3}$ may be given according to the same criteria

Once a course of $P^{32}$ has been completed none is given for at least a year preferably 18 months In most cases relapse occurs in 9 months to 2 years If relapse ensues in less than 18 months phlebotomies are performed to control the dis ease temporarily This therapeutic schedule can keep the to tal dose of $P^{3}$ to a minimum which is important in those patients who are ultimately treated for 15 25 years

► [An excellent and authoritative statement of the problem —Ed ]

**Nosographic Differentiation (Clinical and Hematologic) of Thrombocythemias** is presented by J Mallarme and Ph Auzepy[9] on the basis of published and unpublished series of cases in which the platelet count exceeded 500 000 They consider the following classifications of thrombocythemia (1) in the course of polyglobulism or Vaquez s disease (2) with splenectomy or splenic atrophy (3) malignant or leu kemic myeloses (4) with secondary myeloid splenomeg aly and (5) essential or autonomous They conclude that thrombocythemia should be regarded as an expression of

(9) Sang 28 210 218 1957

hyperplasia of the megakaryocyte platelet series As an expression of a myeloproliferative process thrombocythemia is never isolated but constitutes part of a general panmyelosis affecting the granulocytic and erythroblastic series simultaneously For this reason it belongs under three headings of hematology three aspects of proliferative myelosis

Thrombocythemia of polyglobulism simple hyperplastic myelosis shows an increase of adult elements in peripheral blood and a simple proliferation of myeloid tissue This type is the thrombocythemia of Vaquez s disease along with thrombocythemias caused by splenectomy and splenic atrophy and most essential thrombocythemias The myelosis corresponds to a physiopathologic syndrome of hyposplenism through imbalance of the marrow spleen antagonism [This is pure speculation —Ed ] These are the most frequent cases Thrombocythemia of leukemias malignant dystrophic hyperplastic myelosis shows an increase and cellular dystrophy of the three myeloid series with immature cells in the blood (myelocytes and myeloblasts erythroblasts megathrombocytes and megakaryocytes) and a generalized myelogenous infiltration of the spleen and other tissues Thrombocythemia of myeloid splenomegaly secondary hyperplastic myelosis is sometimes accompanied by proliferation of the reticulum and of the stroma observed in inflammations metastatic cancers Hodgkin s disease osteomyleosclerosis etc In all these varieties thrombocythemia may or may not be productive of hemorrhage this characteristic being subordinate to factors independent of the type of thrombocythemia

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## LUPUS ERYTHEMATOSUS CELL PHENOMENON

► Inclusion of 3 articles concerning this diagnostic phenomenon is justified because it involves leukocytes and relates to a disorder often associated with hemolytic anemia leukopenia or thrombocytopenic purpura —Ed

**Phase Contrast and Interferometric Microscopy of L E Cell Phenomenon.** The L E cell phenomenon considered pathognomonic of systemic lupus erythematosus occurs in two stages (1) a peculiar nuclear alteration in lymphocytic or polymorphonuclear leukocytes producing swollen structureless masses which are the L E bodies and (2) ingestion

of these bodies by viable blood phagocytes to form completed L E cells The primary intranuclear event in the formation of L E bodies is a profound alteration in the nature and quantity of the protein components of the deoxynucleoprotein complex Richard A Rifkind and Gabriel C Godman[1] (Columbia Univ ) studied unstained leukocytes by phase contrast and interference microscopy

The earliest detectable change in the polymorphonuclear leukocyte nucleus 5 15 seconds after addition of L E serum is a sudden uniform homogenization of the normal nuclear pattern The nucleus appears multilobed of uniform density and without visible internal differentiation Each lobe usually becomes one L E body The altered lobes rapidly swell The cell membrane breaks and a swollen nuclear lobe may be partially or totally extruded from the cell forming a characteristic L E body Lymphocytes are similarly affected but the process is slower in inception

The cell cytoplasm and the cytoplasmic granules appear to be mechanically displaced by the expanding L E body and on rupture of the cell may disperse in the suspending medium or remain as a cytoplasmic ghost of the original cell Phagocytosis of the L E bodies occurs if incubation is continued with viable polymorphonuclear leukocytes and optimal yield is attained after about 20 minutes incubation The cytoplasmic material is not grossly phagocytosed

The prerequisites for the L E phenomenon are the presence of injured and nonviable leukocytes L E serum and blood phagocytes The substrate of injured leukocytes is not species specific The differences in the wide variety of L E technics are in the manners in which they achieve the primary injury to the substrate leukocyte

**Affinity between Lupus Erythematosus Serum Factor and Cell Nuclei and Nucleoprotein** was studied by Halsted R Holman and Henry G Kunkel[2] (Rockefeller Inst ) The serum of many patients with systemic lupus erythematosus can alter white blood cells in vitro e g the nuclei of some white cells become swollen and bodies resembling swollen nuclei appear in the cytoplasm of other intact white cells The specific reaction probably involves the cell nuclei and the authors suggest that the responsible serum factor com

(1) J Exper M d 106 607 616 Oct 1 1957
(2) Science 126 162 163 July 26 1957

bines directly with cell nuclei and nuclear nucleoprotein The active factor in L E serum migrates and sediments with the faster portion of the gamma globulin

When various types of nuclei were incubated with L E serums and the nuclei removed by centrifuging the serums lost their ability to induce L E cell formation as noted when subsequently tested against white cells although the total serum gamma globulin showed little change The centrifuged nuclei washed free from protein were readily phagocytosed by fresh human white blood cells to form L E cells



Fg 0—V ual t f L E ell prep r t m d wt L E se m a d t n d wth fl sce t a t b dy to h ma gamma gl b l N t m k d fl s c f w llen wh te c ll cle In d t c l p ep t ns m d w th n m l s um t l o u le fluo e ence was t d. (C t y f H lma H R nd Ku k l H G)

Nuclei exposed to normal serum and treated similarly were not phagocytosed The active absorbed L E factor was found to be a gamma globulin Isolated nuclear nucleoprotein induced the same sequence when incubated with L E serum The strands of nucleoprotein were phagocytosed by normal white blood cells to form inclusion bodies similar to those of L E cells

In further studies the fluorescent antibody technic was used Slides containing L E cells were reacted with fluorescent rabbit antiserum to normal gamma globulin Nuclei that were changing just before phagocytosis and inclusion bodies fluoresced brilliantly (Fig 70) No similar fluorescence of the nucleus of the phagocytic cell or of nuclei in control preparations occurred This demonstrated localization of the gamma globulin presumably L E factor on the affected nuclei during in vitro L E cell formation The data suggest that the L E serum factor has an affinity for nuclear nucleoprotein and that desoxyribonucleic acid is involved in the bond Its reaction with antiserum to normal

gamma globulin suggests that it is an antibody perhaps an autoantibody to nucleoprotein or desoxyribonucleic acid

**Comparative Evaluation of Sensitivity of L E Cell Test Performed Simultaneously by Different Methods** Since the L E cell was first described in 1948 many methods have been described for its demonstration and each has been claimed to be more sensitive than the others Edmund L Dubois and Vivian Freeman[3] (Univ of Southern California) performed a battery of tests on peripheral blood drawn from one venipuncture including examination of the buffy coat forcing a clot which had remained at room temperature 2 hours through a sieve the ring test of Snapper and Nathan and the Zinkham Conley modified technic using rotary beads

In 47 proved cases of systemic lupus erythematosus treated and untreated 63 batteries were performed and 42 were positive in at least one test In 5 only the rotary method was positive in 4 the clotted method and in 2 the ring method The largest numbers of L E cells and hematoxylin bodies were found by the rotary method If only one test is to be performed the rotary method is preferred The use of excessive amounts of heparin over 0 75 mg /10 cc blood depresses the L E phenomenon Heparin should not be added to blood and the use of heparinized syringes to draw the specimens should be avoided

Augmentation of the L E phenomenon by clotting or rotation with glass beads is best explained as the production of leukocyte trauma This explains the poor results when clotted specimens are broken up with wooden applicator sticks rather than macerated through a fine sieve The clotting mechanism itself probably has little to do with the increased numbers of L E cells

With adequate treatment the L E cells disappeared in many patients Forty patients with positive L E cell tests treated 2 months or more had a simultaneous battery performed again All tests were negative in 18 7 had fewer than 5 L E cells/500 leukocytes and 15 patients had more than that number

(3) Blood 12 657 6 0 J ly 1957

**Evaluation of Lymphadenopathy in Systemic Disease** Lymph node biopsy often helps in diagnosis when routine investigation fails Richard D Moore Austin S Weisberger and Edgar S Bowerfind Jr [4] (Western Reserve Univ ) reviewed biopsy specimens from 379 patients with lymphadenopathy Specific histopathologic diagnoses were made in 201 which were correlated well with the clinical impressions Of the other 178 patients 158 were followed clinically for long periods Biopsies had shown hyperplasia in 137 of these inflammation in 16 and normalcy in 5 The clinical diagnoses were collagen disease in 26 malignancy in 33 dermatoses in 12 miscellaneous diseases in 32 and 47 were well on follow up

Enlarged superficial lymph nodes were frequently associated with serious often fatal systemic disease Of the 158 patients in whom the histopathologic diagnosis was not specific only 47 were well 55 died an average of 13 months after biopsy This suggests that patients with lymphadenopathy unexplained by biopsy should be followed carefully for a long time

Histologic diagnosis of hyperplasia was based on finding increased numbers or increasingly less mature cells within the pulp of the lymph node more prominent or numerous sinusoid cells or germinal centers in which mitoses or nuclear debris was present Periodic acid Schiff positive cytoplasm in many plasma cells was frequently found in diseases considered to be the result of antigen antibody reactions The most significant and specific change was found in lymph nodes of patients with disseminated lupus erythematosus—a periodic acid Schiff positive inclusion body within the cytoplasm of some plasma cells Hematoxylin bodies were present only if there was necrosis of lymph node tissue Necrosis of lymph node tissue frequently found in autopsy material was not seen in any of the biopsy specimens

Many patients with lymphadenopathy in whom the histologic findings were nondiagnostic had a recognizable serious illness shortly after biopsy Collagen disease and

(4) A M A Arch I t M d. 99 751 759 M y 1957

malignancy predominated In patients who acquired dissem inated lupus erythematosus hyperplasia of the lymph nodes was fairly characteristic—plasma cells with periodic acid Schiff positive cytoplasm were prominent and all patients had periodic acid Schiff positive inclusions

► [A reminder of the finite diagnostic value of lymph node biopsy and consequently of the physician s responsibility to secure such information in the patient with unexplained lymph node enlargement.—Ed ]

**Induction of Mouse Leukemia with Purified Nucleic Acid Preparations** Recently leukemia with the immunogenetic characteristics of the recipient strain was induced in low leukemia incidence strains of mice by injecting into new borns the cell free extracts of tissues of high leukemia strains The agent is filtrable and thermolabile and transmit ted in some families of mice from one generation to an other directly through the embryos Under certain condi tions extracts of leukemic organs may also produce parotid gland tumors sarcomas and other neoplasms indicating either multipotency or that the extracts contain several on cogenic agents Although this could be due to transfer of discrete infective virus particles it could also be a process analogous to transduction by an agent resembling lyso genic bacteriophage or to bacterial transformation in which the active agent is free desoxyribonucleic acid

Esther F Hays Norman S Simmons and William S Beck[5] (Univ of California) describe a series of experiments in which the incidence of leukemia was apparently increased in a hybrid strain by injecting into newborn mice a purified nucleic acid prepared from the lymphoid tissues of a high leukemia donor strain

The desoxyribonucleic ribonucleic acid from the non leukemic AKR mice and that from animals of the same strain with leukemia was apparently active in producing an incidence of leukemia in the hybrids comparable to that induced by cell free extract injections

The results suggest that free nucleic acid is leukemogenic although it is possible that a virus or provirus may be the active agent in cell free extracts and that the nucleic acid preparations contain active virus nucleic acid It is unlikely however that intact active virus could survive the nucleic acid isolation procedure

**Studies in Leukemia VI Induction of Leukemia in AKR**

(5) N t re London 2 1419 14 0 Dec. 21 1957

**Mice by Means of Cell Free Brain Filtrates of Humans Who Died of Leukemia** A filtrable agent has previously been demonstrated in the brain of AKR and white Swiss mice who had leukemia which was capable of inducing leukemia in homologous animals when injected A similar filtrable agent has been found by Steven O Schwartz Harold M Schoolman Paul B Szanto and Wilma Spurrier[6] (Cook County Hosp ) in the brains of patients dying of leukemia which can accelerate or induce leukemia in AKR mice

Of 326 animals inoculated with cell free filtrates of human leukemic brain 71 acquired leukemia before age 22 weeks The interval between injection and development of leukemia was 2 12 weeks with an average of 3-4 weeks When the filtrates were inactivated by heating at 65 C for 45 minutes or were derived from nonleukemic human brains leukemia did not develop in any of 248 AKR mice inoculated

The incidence of leukemia induced in the AKR mice by inoculation with cell free filtrates of human leukemic brain is of such magnitude as to imply a causal relation The leukemia of the AKR mouse is lymphoblastic whether the disease is spontaneous or induced by filtrates of human leukemic brain even if the source of brain filtrate is from acute myeloblastic leukemia brain This suggests that the type of leukemia induced is primarily a function of the host response The observed facts may also be explained as the filtrate merely accelerating the development of the spontaneous disease which however is very rare in this AKR strain *before 22 weeks of age the time limit adopted for the trials*

**Problem in Diagnosis of Leukemia** In early cases agranulocytosis aplastic anemia myeloid metaplasia or hypersplenism must be excluded At this point bone marrow aspiration may confirm or deny the eventual diagnosis but some aspirates may not be diagnostic for up to 27 months Manuel J Rowen[7] (Elizabeth N J ) presents 2 more cases in which diagnosis was difficult Though the clinical course signs and symptoms were suggestive of leukemia the diagnosis was not made until the patients were nearly dead

Man 66 had weakness pallor easy bruising and shortness of breath for 2 3 months He was pale acutely ill and had hematomas of the back and arms and pitting edema of the ankles The red blood cell

(6) Ca R 17 218 221 Ap 1 1957
(7) A n. I t. M d. 46 907 914 M y 1957

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**Studies in Leukemia VI Induction of Leukemia in AKR**

(5) Natu e London 2 1419 14 0 Dec. 21 1957

ceeding the statistically expected frequency arouses specu lation that the deleterious stress leading to developmental anomalies of mongolism also triggers the maldevelopment of the blood dyscrasia The leukemia may develop many months postnatally but the essential damage may have oc curred during the neofetal development

CASE 1—In girl aged 22 months acute lymphocytic leukemia was proved by bone marrow biopsy General physical and mental devel opment was retarded She was pale with mongoloid facies several petechiae open fontanels and generalized adenopathy The eyes were slanted and epicanthic folds were present The spleen was palpable 4 cm. and the liver 5 cm below the costal margins The disease course was downhill and she died 7½ months after onset of the acute phase Autopsy confirmed massive leukemic infiltrations in most organs

CASE 2—Girl aged 16 months with characteristic mongoloid fa cies marked pallor and generalized edema was acutely ill The liver and spleen were enlarged Acute myeloblastic leukemia was diag nosed by peripheral smear and bone marrow a piration

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**Intravascular Erythrocyte Aggregation (Sludged Blood) in Multiple Myeloma** was studied by Alberto M Marmont Franco A Fusco Aldo Gay and Lorenzo Mariotti[9] (Univ of Genoa) by taking serial still electronic flash photomicro graphs of blood flow in the superficial vessels of the bulbar conjunctiva from the limbus to the inner or outer angle of the eye through a Goldman biomicroscope Nail bed circu lation was observed with an ordinary capillary microscope *Twelve patients with multiple myeloma exhibited the elec* trophoretic abnormalities typical of the disease

In vitro autoaggregation was marked but was readily dis pelled by addition of saline Hayem s solution caused floc culation of a fine particulate protein precipitate and freed the red cells from their viscous coating The sedimentation rates were high In vivo blood flow in the superficial vessels of the bulbar conjunctiva showed typical intravascular ag gregation (Fig 71) which was not influenced by cold or intravenous heparin and only slightly reduced by large vol umes of intravenous saline These findings were considered identical with the well known sludging phenomenon Though nonspecific they are a constant finding in multiple

(9) Act haem t. 18 49 58 1957

count was 1 300 000 white blood cells 5 400 with a differential of 46 segmented neutrophils 3 stabs 4 eosinophils 40 lymphocytes 1 baso phil and 6 monocytes The platelet count was 15 000 Bone marrow aspiration showed marked hyperplasia of all elements including megakaryocytes He was treated with blood ACTH and a low sodium diet The spleen became palpable and with the diagnosis of hypersplenism was removed It was friable and enlarged and infil trated with leukemic tissue The patient s downhill course contin ued with profuse bleeding conspicuous and he died 4 months later A repeat bone marrow aspiration was surprisingly normal 2 months after diagnosis had been made by histology of the spleen

Bone marrow aspiration is an important tool in the diag nosis of leukemia It is easy to perform, serious side reac tions are few and the pathologic process can be seen micro scopically Classically, leukemia is ruled out or confirmed on the basis of bone marrow evaluation However, there are occasional cases in which a diagnosis is missed because the marrow is apparently normal Leukemia may occur in a greatly disguised form yet pursue a typical clinical course

► [In our experience chronic monocytic or histiocytic leukemias in adults past middle age have been especially difficult of diagnosis Nevertheless, in contrast to localized and therefore surgically or radiologically curable malignant disease there is little advantage in early certainty concerning the diagnosis of leukemia Experienced hematologists know that any un explained anomaly of the peripheral blood may mean leukemia If they are also wise they will keep their suspicions to themselves until symptoms appear or discreet laboratory studies confirm an anxiety for the physician that the patient has been spared —Ed ]

**Acute Leukemia and Mongolism Report of Two Cases** is presented by Wataru W Sutow and Virginia C Welsh[8] (Univ of Texas) The possible biologic significance of si multaneous acute leukemia and mongolism in children was emphasized recently in reports of 20 cases Of 5 cases in which both conditions were found 4 were seen within 1 year a possible chance occurrence of 1 10 000 000 or to be ex pected once in 50 100 years In another survey of 255 chil dren with mongolism 4 cases of acute leukemia were found an incidence much higher than expected in the general pop ulation

The pathogenesis of acute leukemia in children is un known The cause of mongolism too is obscure However exposure in utero to radiation has been etiologically related to mongolism as well as of course to leukemia The coin cident occurrence of the two conditions in numbers far ex

(8) J Ped at. 52 176-181 F b uary 19 °

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(8) J Ped t 52 176 181 F b uary 1958

pattern Subsequent to the original report 18 cases have been reported Four more are presented by Nicholas H Martin and H G Close[1] (London)

The ultimate diagnosis depends on ultracentrifuge analysis but the condition may be suspected if fresh blood exhibits excessive rouleau formation the fresh serum is excessively viscous at room temperature or produces a definite protein precipitate when diluted with 20 times its own volume of freshly distilled water and the precipitate is soluble in 0 15M sodium chloride solution

One patient when first seen had been ill for 2 years and the spleen was easily palpable but ultracentrifuge analysis of the serum was negative Some months later as the disease progressed anemia developed and the albumin globulin ratio was reversed The electrophoretic pattern resembled that of patients with myelomatosis but ultracentrifuge analysis demonstrated abnormally large globulins A precipitate formed when the serum was diluted with 20 times its own volume of water Biopsy of the spleen suggested a diagnosis of pleomorphic reticulosis The histologic findings and clinical picture indicated that the anemia probably was due to stifling of the bone marrow by the turgid macromolecules The macromolecules probably contributed to the more rapid downhill course ending in coma and death but they probably were not the primary disease

Material collected from these 4 patients had only one histologic feature in common an increase in cells the cytoplasm of which was rich in pyronine positive material (plasma cells) This is common in most conditions associated with hypergammaglobulinemia whether or not an excess of macroglobulins is present On clinical and histologic grounds there is little justification for the separation of a disease entity macroglobulinemia

► [In other words this condition like multiple myeloma is primarily a neoplasm of one or more types of anomalous protein producing lymphocytes or plasma cells This concept is clearly set forth by the observations in the next article —Ed ]

**Malignant Lymphoma and Lymphatic Leukemia Associated with Myeloma Type Serum Proteins** H A Azar W T Hill and E F Osserman (New York) report 13 cases and establish the histologic criteria to differentiate this group

(1) Lancet 2 8-12 July 6 1957
(2) Am J Med 23 239 49 August, 1957



F g 71 —C f h ghly dysprotein m pl smacyt ma L g ch g gg g tes a e ı ble n e us cha nels nt p ced by gul r l ar plasm p es wh eas g s clump ng n rt ri le p e e t d by peed of flow (Cou te y f M rm t A M t l A ta h mat 18 49 58 1957 )

myeloma associated with gross serum protein abnormalities involving molecular anisodiametry Although no throm bosing tendency was observed 2 of the patients showed myeloma purpura

Macroglobulinemia has been reported in such diverse cases as to raise doubt that these large molecules in the cir culation are pathognomonic of one syndrome In 1944 Wal denstrom described 2 cases in which the serum was unusu ally viscous at room temperature and contained large amounts of gamma globulin Ultracentrifuge analysis dem onstrated a protein with a sedimentation coefficient of 19 20 Svedberg units (Normal gamma globulin is about 7 units ) The clinical picture described was that of an old person usually a man with years of gradually increasing weakness and dyspnea The most dramatic features such as hemor rhage from the mouth epistaxes and symptoms of Ray naud s disease have not been consistently present in subse quent cases Objective findings were a palpable spleen nor mochromic anemia some weight loss and a markedly in creased erythrocyte sedimentation rate However the fea ture considered essential to the syndrome was the unusual qualitative and quantitative changes in the serum protein

components Transitional forms between reticulum cells lymphocytes and plasma cells have been observed and designated as undifferentiated reticuloendothelial cells lymphoid cells plasma cell variants or pyroninophilic mesenchymal cells They were also observed in this study (Fig 72) and it is suggested that these cells represent immature myeloma cells or plasma cell precursors Pyroninophilia though not a specific property of the plasma cell series may indicate increased intracytoplasmic synthesis or storage of gamma globulin Plasma cells may be forms of lymphocytes and reticulum cells in which qualitative or quantitative alterations in nucleoprotein metabolism have occurred

Plasmacytosis or many pyroninophilic reticulum and lymphoid cells in tissue sections and/or bone marrow aspirates were characteristically found in patients with malignant lymphoma and lymphatic leukemia who had the abnormal serum proteins usually found in multiple myeloma Other patients with these diseases but with normal serum proteins had no significant plasmacytosis or pyroninophilic reticulum and lymphoid cells Clinically and morphologically transitional forms occur with considerable overlapping between the various lymphatic tumors and the plasmacytomas

**Myelofibrosis Complicated by Lymphogenous Leukemia** It is often difficult to differentiate between *myelofibrosis* chronic myelogenous leukemia and some types of polycythemia vera One such disturbance may develop into another Originally myelofibrosis was distinguished from chronic myelogenous leukemia (aleukemic or subleukemic) and called erythroleukemia or nonleukemic myelogenous splenomegaly Such syndromes usually originate as idiopathic myelofibroses Occasionally myeloma proteins may be disclosed by electrophoresis or the number of lymphocytes in the blood may indicate a lymphogenous leukemia substantiated by lymph node biopsy or splenic puncture Aage Videbaek and Hemming Poulsen[3] (Univ of Copenhagen) report a case of typical myelofibrosis complicated by lymphogenous leukemia

Man 44 ill for 3 years with weight loss recurrent renal colic and anemia had required many transfusions The spleen and liver were markedly enlarged The peripheral blood showed normochromic

(3) Act h m t 17 250 256 195

from the common or usual variety of malignant lymphoma

The predominant histologic feature was proliferation of lymphoid and reticulum cells Marked plasmacytosis was observed in 6 patients Of the other 7 1 showed strongly pyroninophilic reticulum cells resembling immature myeloma cells 3 had lymphoid cells which contained abundant cytoplasm with a strong affinity for pyronin and 3 were incompletely studied but the histologic picture was that of a

Fg 72—C l lymph ode Typ l m t e pla ma lls ( w ) sc tt ed am g lymphocyt wh ch f m p ed m t cell type Lymph d lls w th fairly b da t cyt pl m d som h mat l mp g p bably p nt t t on f rms between lymphocyt and pla m cells H m to yl d d f m ×1000 (Cour t y f A H A t l Am J M d 23 239 249 A gu t 1957 )

lymphosarcoma or lymphatic leukemia without any differentiating features such as abundant cytoplasm or pyroninophilia Plasmacytosis when present was usually demonstrated in most of the tissues involved by the disease Transitional forms between reticulum cells and lymphocytes and plasma cells were frequent (Fig 72)

Accumulations of plasma cells in bone marrow and lymph tissue are associated with hyperglobulinemia With agammaglobulinemia plasma cells are virtually absent from the bone marrow and lymph nodes It is yet unknown whether lymphocytes and reticulum cells in the absence of plasma cells and their direct precursors can synthesize globulin

mixture Aerobic glycolysis oxygen uptake and carbon di oxide production were measured in Warburg and Summerson manometers in white cell suspensions to which had been added glucose and the chemotherapeutic drug to be tested

Acute leukemic blast cells exhibit significant aerobic glycolysis in vitro thus supporting the concept that leukemic cells are truly cancer cells When leukemic cells were incubated with certain chemical agents metabolic changes occurred which were reproducible and the response appeared to be a function of the cell type Methotrexate 6-mercaptopurine hydrocortisone triethylene thiophosphoramide and 6-azauracil usually inhibited aerobic glycolysis of acute lymphatic leukemia cells but not the blast and other abnormal cells from patients with acute myelogenous leukemia These observations are consistent with the clinical impressions of the value of methotrexate in inducing remissions in acute lymphatic leukemia and the rarity of its beneficial effects in acute myelogenous leukemia

That 6-mercaptopurine occasionally inhibited aerobic glycolysis in acute myelogenous leukemia is consistent with the clinical finding that it is the drug of choice for this disorder Leukocytes from 3 patients with leukocytosis but not leukemia also showed no inhibition of glycolysis by antileukemic agents

Certain glucose analogues such as 2 desoxyglucose and 2 desoxygalactose are potent glycolytic inhibitors of acute myelogenous leukemia cells K 2 carcinoma ascites cells and other tumor cells Folic acid Teropterin® methotrexate and 6 mercaptopurine may also have such effects Profound glycolytic inhibition is obtained in mouse melanoma mitochondria with methotrexate or 6 mercaptopurine and this can be overcome by increasing the concentration of adenosine triphosphate or by substituting glucose-6-phosphate for glucose in the substrate All these structurally related compounds are thought to act by interfering competitively with adenosine triphosphate in glucose phosphorylation by the hexokinase reaction

**Remissions Induced by Chlorambucil in Chronic Granulocytic Leukemia** Busulfan (Myleran®) has been effective in depressing the granulocytes in patients with chronic granulocytic leukemia and chlorambucil in depressing the lymphocytes in chronic lymphatic leukemia and Hodgkin s dis

anemia thrombocytopenia and immature myelogenous cells and erythroblasts Bone marrow aspiration produced only peripheral blood Bone marrow biopsy revealed myelofibrosis The spleen was removed but the patient died from oozing hemorrhages from the numerous adhesions detached from the surface of the huge spleen.

The autopsy bone marrow was grayish to gray red solid and tough Histologically fibrosis was most pronounced in the femoral shaft and sternum The marrow contained cellular areas with accumulations of uniform cells similar to lymphocytes Granulocyte precursors and some reticulum cells were found and some megakaryocytes but only slight erythropoiesis Some mediastinal and abdominal lymph nodes showed complete obliteration of structure with tightly packed lymphocytes with scarce cytoplasm The kidneys showed typical leukemic nodules The spleen showed widespread fibrosis with decrease in lymphatic tissue and in the number of reticulum cells Extramedullary hemopoiesis was diffuse

The diagnosis of myelofibrosis was made by bone marrow biopsy Lymphogenous leukemia was not diagnosed until autopsy but might have been suspected when the white blood cell count revealed 45% lymphocytes and the splenic smear contained 84% Myelofibrosis typically pronounced in bone marrow and spleen prevented these organs from reacting in the manner expected in lymphogenous leukemia

► [Or conceivably because of the many clinical and experimental circumstances in which myelofibrosis develops there may have been a late and nonspecific response to an initial lymphoid process —Ed ]

**Effects of Chemotherapeutic Agents on Metabolism of Human Acute Leukemia Cells in Vitro** No chemotherapeutic drug has universal applicability to patients with cancer Even within a single category such as acute lymphatic leukemia response to an antimetabolite is unpredictable John Laszlo James Stengle Kent Wight and Dean Burk[4] (Nat l Inst of Health) devised a screening method for chemotherapeutic drugs that depends on their effect on glycolysis of leukocytes from patients with leukemia Aerobic glycolysis is a universal property of all cancer cells thus far studied Inhibition of tumor growth in vivo parallels the glycolytic inhibition in vitro For these reasons glycolysis is an ideal indicator of metabolic antitumor activity Leukemia is ideally suited to such studies because it can be serially sampled and the selected material is almost devoid of contaminating tissue cells

Patients with high white blood cell counts mostly blast and abnormal cells were selected Blood was drawn in a heparinized syringe and allowed to sediment in a fibrinogen

(4) P oc S c Expe B l & Med 97 127 131 J rv 1958

terone bone pain fever chills nausea and vomiting were induced The effects were analogous to the alcohol reaction frequently seen in patients with Hodgkin s disease but were more severe Edward Shanbrom and Stuart C Finch[6] (Yale Univ) cautiously investigated this phenomenon in 11 other patients with various malignant lymphomas When it became apparent that methyltestosterone was inducing a severe clinical relapse in some further studies in humans were stopped The effect is now being studied in experimental rodent lymphomas

CASE 1—Man 39 had pain in the chest lumbosacral area and right hip X rays revealed bony lesions Hodgkin s disease was proved On phenylbutazone he returned to full time work and his only complaint was impotence He was given buccal lozenges containing 5 mg methyltestosterone 3 times daily but within 2 days noted nausea and recurrence of pain He increased the dose of phenylbutazone which relieved the pain but on the 3d day of testosterone the pain was no longer relieved The acute symptoms including nausea and vomiting subsided when testosterone was stopped

CASE 2—Man 63 had a macrofollicular lymphoma with bilateral pleural effusions and a large mediastinal mass which re ponded to radiation therapy and thoracenteses He was in fairly good health He was given 10 mg methyltestosterone twice daily for 2 days and suddenly had nausea vomiting chills profuse sweating epigastric distress and severe low back pain Symptoms were most severe 1/2 hours after taking of the drug then gradually subsided except that the back pain and epigastric distress persisted

CASE 3—Man 51 with lymphoblastic lymphosarcoma was treated with nitrogen mustard and was in fair health He was given methyl testosterone 10 mg twice daily for 2 days By the end of the 2d day he felt nauseated and vomited Most striking was the onset of generalized bone pain and tenderness especially at the sites of previously known iliac involvement

CASE 4—Woman 31 had Hodgkin s disease She was tested with 20 mg methyltestosterone daily for 3 days After the 2d dose she had fever nausea malaise anorexia severe generalized pain and profuse diarrhea

CASE 5—Man 26 had Hodgkin s disease and was given 20 mg methyltestosterone daily for 6 days In the next few days he had a sharp increase in symptoms fever chills profuse sweating increase in cough anorexia and extreme lethargy

The prerequisite for an adverse reaction appears to be the presence of an advanced form of widespread lymphoma Hemolysis was not apparent in any of the reactions but all except 1 of the tested patients developed anemia after the

(6) C 10 964 9 0 S pt O t 1957

ease These alkylating agents seem to have separate and specific effects in these conditions If this is correct it would be highly significant since chemical modifications of poly functional alkylating agents could then be designed to in hibit specific proliferating tissues This thesis was not sup ported by satisfactory clinical data as no studies have been reported on the use of busulfan in chronic lymphatic leu kemia or of chlorambucil in chronic granulocytic leukemia.

Irwin H Krakoff David A Karnofsky and Joseph H Burchenal[5] (New York) report 2 cases of chronic granulo cytic leukemia in which the disease was satisfactorily con trolled with chlorambucil

CASE 1—Woman 26 had chronic granulocytic leukemia A brief course of busulfan (7 doses of 4 mg ) and mercaptopurine (8 doses of 50 75 mg ) induced a transient fall in leukocytes The white blood cell count returned to 206 000/cu mm and the spleen was palpable 16 cm below the costal margin Chlorambucil was started 8 mg daily and leukocyte and differential counts gradually returned to normal The spleen became barely palpable On 4 mg chlorambucil daily she has remained in good remission

CASE 2—Woman 34 had splenomegaly to 22 cm below the costal margin and typical blood and marrow findings of chronic granulo cytic leukemia Chlorambucil 8 mg daily resulted in a gradual fall in leukocyte count and a decrease in spleen size On a maintenance dose of 8 mg daily she remained in good remission although the spleen could still be palpated

The polyfunctional alkylating agents have been modified to minimize nausea and vomiting and other undesirable side effects but they have not been modified to the degree that one alkylating compound will produce a greater therapeutic ef fect with less bone marrow toxicity act against one type of neoplastic disease not affected by another or produce a re mission in a patient who has become refractory to one of the other polyfunctional alkylating agents Busulfan is not specific for myeloid tissue in man It can induce good remis sions in chronic lymphatic leukemia and malignant lymph oma The 2 cases reported here demonstrate that chlorambu cil which is effective in chronic lymphocytic leukemia pro duces entirely satisfactory response in early chronic granu locytic leukemia

**Adverse Effects of Methyltestosterone in Lymphomas** In an attempt to alleviate impotence in a patient with wide spread Hodgkin s disease by administering methyltestos

(5) J A M A 166 629 630 Feb 8 1958

findings such as the crossing of megakaryocytes by leukocytes and the presence of red blood cells in the cytoplasm of megakaryocytes were also similar to those in the controls In striking contrast to normal bone marrow cultures daily separation of platelets revealed a steady decrease in number and a corresponding decrease in serotonin binding capacity Furthermore degenerative changes in the platelets such as swelling and concentration of the granules in one portion of the hyalomere were seen often among the thrombocytes after separation from bone marrow tissue Direct observation gave the impression that actively moving cells phagocytosed large numbers of platelets Isolated platelets rarely were encountered but a few masses of agglutinated thrombocytes were seen

When normal bone marrow was cultured with antiplatelet serum the process of thrombocytopoiesis was similar to that in bone marrow cultures of patients with purpura Within 4-5 hours almost all megakaryocytes broke down and the platelets thus produced were seen in the form of clumps Almost no inactive megakaryocyte could be found Daily separation of platelets revealed even more striking decrease in their number and serotonin binding capacity than in the marrow cultures of patients with purpura Most platelets microscopically examined showed signs of degeneration Many platelets apparently underwent phagocytosis

These observations furnish further evidence of the importance of platelet agglutinins in the pathogenesis of idiopathic thrombocytopenic purpura Admittedly tissue culture is an artificial set up and not necessarily similar to the process in the bone marrow in idiopathic thrombocytopenic purpura However since the pattern of changes fits the general pattern of the pathogenesis of this disease it seems probable that the conclusions made are applicable to the conditions pertaining in vivo

**Differentiation of Antiheparin and Thromboplastin Generating Factors in Human Platelets** *John V Garrett and Edmund Klein*[8] (Harvard Med School) proved these are two separate factors

METHOD—Lyophilized human platelet material was prepared and extracted with alcohol ether and the thromboplastin generating material precipitated by adding 3 volumes of acetone in the cold The precipitate was suspended in a small volume of water and lyophi

(8) P oc Soc E pe B l & M d 96 8-3 8 5 D cembe 1957

testosterone trials The calculated rate of erythrocyte destruction was at least two to three times normal during the 2 3 weeks after the trials Local pain at the site of bone lesions and the other constitutional effects attributed to the tumor may have been due to changes in tissue adjacent to the tumor

Androgens are known to be tumorigenic in man e g prostatic carcinoma If methyltestosterone effects in lymphomas point to adverse effects of body androgens reducing eliminating or neutralizing endogenous androgens may benefit.

► [Painful bone crisis presumably due to an acute proliferation of the marrow has been recently reported by Jandl as an effect of folic acid in pharmacologic dosage in a patient with Mediterranean anemia and megaloblastic bone marrow —Ed ]

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## THROMBOCYTOPENIC AND VASCULAR PURPURAS

**Studies on Thrombopoiesis II Thrombocytopoiesis in Vitro from Bone Marrow of Patients with Idiopathic Thrombocytopenic Purpura** Previous studies of thrombocytopoiesis in tissue culture of normal human and animal bone marrow showed that megakaryocytes produce a large number of viable platelets in 24 60 hours G Izak and D Nelken[7] (Hebrew Univ ) studied thrombocytopoiesis from megakaryocytes in bone marrow cultures of 3 patients with idiopathic thrombocytopenic purpura Studies also were made of thrombocytopoiesis in cultures of normal bone marrows incubated with antiplatelet serums

The number of megakaryocytes in the bone marrow from the 3 purpura patients appeared much greater than in normal marrows previously studied The cells were of various sizes mostly round and without degenerative changes The process of thrombocytopoiesis was similar to that in normal marrows but coarse granules appeared aggregated in irregular massive cords and broke down into platelets more rapidly than normal In some instances the process in all cells seen was completed in 12 16 hours as against the 48-60 hours required in normal bone marrow The number of inactive cells was similar to that in normal marrow Other

(7) Blood 12 520 528 J ne 1957

blood is mixed with 2 ml of 3 8% sodium citrate solution and centrifuged at 800-1 000 rpm for 10 minutes The (platelet rich) plasma is obtained and direct platelet counts are made The plasma is then centrifuged at 3 000 rpm for 15 minutes and the button of platelets washed 3 times in normal saline. The platelets are then resuspended in saline at a concentration of 1 600 000/cc. A similar suspension is made of normal platelets at the same time Thromboplastin generation tests are then applied using normal serum

The degree of hemorrhage or purpura and the platelet count were recorded at the time the platelet function tests were performed When platelet thromboplastic function was below 12% all patients were frankly bleeding between 12% and 25% some patients were hemorrhagic while others showed purpura only above 25% virtually no patients *were hemorrhagic Purpura occurred over the range 25 53%* platelet thromboplastic function

Hemostasis depends on three main factors (1) the efficiency of the vascular mechanism including the ability of vessels to contract and the effects of serotonin (2) the degree of damage to the vascular endothelium and (3) the effectiveness of the coagulation mechanism The last two are important in the spontaneous hemorrhages of thrombocytopenic purpura The reduction in platelets is not the prime factor With sufficient vascular damage frank bleeding seems to be directly related to the degree of platelet thromboplastic dysfunction or when there is an additional serum thromboplastic defect to the total thromboplastic efficiency Assuming that the same factor produces both vascular and platelet functional defects the degree of each would be roughly proportional The platelet function test would then give an approximate estimation of both the degree of vascular damage and the state of the coagulation mechanism

► [A valuable addition to a difficult topic.—Ed.]

Studies of Hemostatic Mechanisms in Leukemia and Thrombocytopenia The bleeding tendency associated with leukemia is poorly correlated with platelet counts and other hemorrhagic manifestations Hematologic abnormalities such as fibrinolytic activity circulating anticoagulant hypofibrinogenemia and thrombocytopathia are so infrequent they cannot contribute to the bleeding dyscrasia in most patients with leukemia Jessica H Lewis Joseph H Burchenal Rose R Ellison John H Ferguson Jeffress H Palmer M Lois Murphy and Marjorie B Zucker[1] intensively

(1) Am. J Clin P th. 8 433 446 N mbe 1957

lized This lyophilized material was suspended in imidazole buffer pH 7 4 to a concentration of 1 mg /ml This is the platelet lipid extract containing thromboplastin generating activity The residue of platelets after lipid extraction was freed of organic solvents and resuspended in imidazole buffer to a concentration of 3 mg /ml The brain lipid extract was the alcohol ether soluble acetone precipitated cephalin fraction of beef brain

The various materials were tested to determine their activity on heparin at different stages in the coagulation process 6 mg lyophilized human platelet material or lipid extracted platelets completely neutralized the effects of 0 1 unit of heparin similar to equivalent amounts of fresh platelets

Thromboplastin was generated rapidly when the lipid extracted from platelets was used but only a small amount of thromboplastin was formed slowly after heparin was added to the system Formation of thromboplastin was restored to nearly normal by adding lipid extracted platelet material to the system This lipid extracted material did not itself have any *thromboplastin generating potential However* when used alone it was partially effective in neutralizing heparin in the earlier stages of incubation Similar results were obtained when brain lipid extract was used in place of the platelet lipid A combination of brain lipid extract and lipid extracted platelets reversed the effects of heparin Whole platelets have the same anti heparin effect as the combination of brain lipid and lipid extracted platelet material

Platelet materials have no accelerating effect on the thrombin time alone but in suitable concentrations antagonize the effect of heparin on it The heparin antagonizing fraction does not in itself possess any thromboplastic activity but it reverses the effects of heparin on thromboplastin formation and thrombin activity The material responsible is present in an aqueous extract of lipid extracted platelets

**Studies of Platelet Function as Guide to Severity of Thrombocytopenic Purpura and Possible Mechanism of Purpura and Hemorrhage** The severity of thrombocytopenic purpura and the response to therapy cannot yet be tested by any single method The platelet count is often dissociated from hemorrhagic manifestations J A Bonnin[9] (Adelaide) demonstrated *the usefulness of the study of platelet thromboplastic* function in assessing the severity of the disease in 30 patients

Method—Drawn into silicone glass 18 ml of the patient s venous

(9) A t L Ann M d. 6 196-202 A g t 1957

in platelets and is dangerous as an emergency measure during acute bleeding Use of siliconized bottles or plastic bags for transfusion of fresh whole blood has preserved viable platelets and use of ACTH and corticosteroids has recently been successful in controlling the hemorrhagic crises William Dameshek Fernando Rubio Jr John P Mahoney W Harrison Reeves and Leonard A Burgin (Boston) report 30 consecutive cases treated for 24 months Prednisone (Meticorten®) was given orally in divided doses initially 20 250 mg/day and then decreased gradually to 2 5 15 mg/day or withdrawn entirely after normal platelet counts had been induced

A normal platelet count was attained in 6 150 days in 22 cases—in 10 of the 11 acute cases after an average of 22 4 days of treatment and in 12 of the 19 chronic cases after an average of 50 days In 2 other chronic cases the platelet count reached nearly normal levels Improvement occurred in 2 of the other 6 cases and there was little or no change in 4 When the dose of prednisone was reduced the platelet count frequently declined also When relapse occurred after withdrawal or reduction of the dose therapy with higher doses again induced excellent responses in 10 20 days In 4 of the acute and 4 of the chronic cases prednisone therapy was eventually discontinued without decrease in the platelet count

The effect of prednisone in raising platelet levels in patients with idiopathic thrombocytopenic purpura is consistent and striking The mechanism is unknown Results with prednisone are relatively certain and predictable in contrast with the uncertain effects of even large doses of ACTH and cortisone The disease may be considered as an autoimmune disorder arising by some obscure antigenic stimulus and attacking the patient s own platelets In acute cases the antibody probably develops suddenly attacks explosively and often disappears but in chronic cases the immunologic mechanism is probably self perpetuating resulting in chronic thrombocytopenia The disease is often a prodrome of lupus erythematosus

In treatment prednisone and fresh plastic bag transfusions should be emphasized Splenectomy should be reserved for severe cases that do not respond to these measures It is

(2) J A M A 166 1805 1815 Ap 12 1958

studied the hemostatic function in patients with various forms of leukemia with and without hemorrhagic manifestations in patients with thrombocytopenia from other causes and in 3 with thrombocythemia

Some patients with low platelet counts had no hemorrhagic difficulties whereas others with nearly normal counts had fairly severe bleeding Deficiencies of plasma factors particularly proaccelerin were frequent but were not well correlated with the degree of bleeding tendency

In leukemia the megakaryocytes were reduced in the bone marrow when the platelet count was low In chronic idiopathic thrombocytopenic purpura they were frequently increased but seemed immature and platelet formation was rare In acute idiopathic thrombocytopenic purpura the megakaryocytes were sometimes scarce and relatively normal in appearance The 3 patients with thrombocythemia had greatly increased numbers of megakaryocytes and active production of platelets

When patients with leukemia were compared with those who had other causes of thrombocytopenia the most striking difference was in the results of tourniquet tests Tests of most patients with leukemia were negative In those with idiopathic thrombocytopenia tests were impressively positive

Prothrombin consumption was abnormal in all instances in which the platelet count was less than 50 000/cu mm In thrombocythemia a great increase in the platelet count was frequently accompanied by a relative depression in platelet function and a decreased amount of plasma proaccelerin Abnormalities in clot retraction and prothrombin consumption were well correlated with the platelet count in both groups of patients The level of serotonin in the serum was normal in a few patients with idiopathic thrombocytopenic purpura but low in most of those with thrombocytopenia or leukemia Active fibrinolysin and prolonged plasma thrombin clotting times were observed in some patients with leukemia The precise cause of the hemorrhagic tendency frequently associated with leukemia is still unclear It seems to be correlated with a deficiency of platelets but other factors are involved in many or all patients with leukemia

► [See the preceding article for further study of this problem —Ed.]

**Treatment of Idiopathic Thrombocytopenic Purpura with Prednisone** Splenectomy induces only temporary increase

in platelets and is dangerous as an emergency measure during acute bleeding Use of siliconized bottles or plastic bags for transfusion of fresh whole blood has preserved viable platelets and use of ACTH and corticosteroids has recently been successful in controlling the hemorrhagic crises William Dameshek Fernando Rubio Jr John P Mahoney W Harrison Reeves and Leonard A Burgin (Boston) report 30 consecutive cases treated for 24 months Prednisone (Meticorten®) was given orally in divided doses initially 20 250 mg/day and then decreased gradually to 2 5 15 mg/day or withdrawn entirely after normal platelet counts had been induced

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(2) J A M A 166 1805 1815 Ap 12 1958

not necessary to achieve completely normal platelet counts as patients can enjoy full normal activity without danger of hemorrhage at a platelet level one third to one half that of normal These levels can often be attained with small maintenance doses of prednisone

► [This is a useful appraisal of an extensive experience Prednisone is probably more certain in its action than cortisone because it can be given in larger therapeutic dosage with fewer side effects —Ed ]

**Effect of Stored Blood Transfusions on Platelet Levels in Patients Undergoing Surgical Procedures** was studied by J F Mustard[3] (Univ of Cambridge) in 62 patients Platelets were counted ½ hour before each patient s operation and after each bottle of blood was administered then every other day postoperatively Platelet counts and alumina absorbed plasma thromboplastin activity were determined on each unit of blood before given

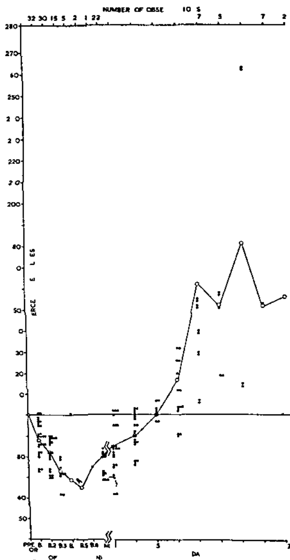
About half the 62 patients receiving whole blood transfusions demonstrated a decrease in circulating platelet levels (Fig 73) None of 10 patients who received blood collected through silicone coated taking sets had any decrease in platelets The average decrease in patients whose platelets decreased was 12% after the first bottle with a further decrease after a third and fourth bottle During the 1st to 3d postoperative days the platelet levels increased and reached a maximum during the 2d and 3d weeks

All patients who exhibited signs of a reaction such as chills marked pyrexia pain in the lumbar region severe headaches and urticarial rashes were excluded There was no obvious relation to the rates at which the transfusion was given and no apparent dilution effect which might account for differences in platelet counts

A subsequent decrease in a patient s platelets was apparently due to transfusion of stored whole blood which had a diminished number of platelets and a low plasma thromboplastin activity Because these changes are characteristic of blood coagulation serum [in unspecified amounts—Ed ] was given to 16 additional patients Each showed a prompt decrease in circulating platelets to levels averaging 86% of the initial

Neither dilution effect nor antiplatelet antibodies ap

(3) Acta h mat 18 80 97 1957




F g 73 —T an f d g l p t t h w g pl t l t d Pl t l t l f h f t p d p t g f p pe t h n f ll w g h bottl f bl od g th d y f p t n d d g p t p t t rv l B1 B6 d t b f bottl f blood g Fl t l t l t l hou th d t m d l h ft t f t h pat t w t pped (C rt y f M s- d J k A t h m t 18 80 97 1957 )

peared adequate to explain the observations In stored blood the changes in platelets antihemophilic globulin factor V and factor VII are similar to those which occur with blood coagulation The evidence indicates that alteration in the thromboplastin factors of blood during storage is associated with thrombocytopenic activity which when the blood is transfused causes a decrease in the recipient s platelets

**Attempted Passive Transfer of Thrombotic Thrombocytopenic Purpura** Since idiopathic thrombocytopenic purpura can be passively transferred by the infusion of plasma T E Brittingham III and Hugh Chaplin Jr[4] (Washington Univ ) attempted a similar experiment by infusing 500 ml plasma from a patient with proved thrombotic thrombocytopenic purpura into a normal volunteer

The recipient s hemoglobin red cell count reticulocytes platelet count white cell count and differential remained normal thereafter He was afebrile and asymptomatic In vitro tests for antibodies were negative Ten months after infusion there was still no evidence of transmission of any disease in the recipient At autopsy the donor showed multiple homogeneous eosinophilic occlusive and partially occlusive lesions in small arteries arterioles and capillaries in many organs Microinfarcts were associated with some of these lesions in the heart and brain One similar experiment in which 250 ml plasma from a patient with thrombotic thrombocytopenic purpura was transfused into a normal recipient has been previously reported No significant thrombocytopenia developed in that instance either

► [Becau e the vascular occlusions have been considered by some to be platelet thrombi the lack of a thrombocytopenic factor in this condition is of special interest —Ed ]

**Histopathogenesis of Rendu Osler Hereditary Hemorrhagic Telangiectasia** F Nodl[5] (Univ of Cottingen) reports on a woman aged 31 with a so called solitary case of Rendu Osler disease in which epistaxis appeared after development of permanent ectasias Tissue from the skin of the back was studied The angioma like telangiectasia was based on a convolution of blocked vessels with structural characteristics delineated in serial sections

The convolution has a distinctive structure and extends

(4) Blood 12 480 482 M y 1957
(5) A h. kl n u expe D rm t. 04 213 235 1957

from the subpapillary venous plexus to the subcutis (Fig 74) Subepidermal ectatic venules are connected with a vascular ramification that consists of several thick bifurcations lying behind one another At the point of departure of most branches but also in straight portions are ringlike coverings of longitudinal muscle cells At such places the lumen is narrow and in between often widened and spindle like so that these vessels have a beadlike appearance Nearby and in the deepest portion there is also more pronounced vascular widening resulting from lateral building of a wall seg

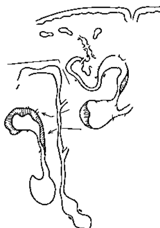


Fig 74 —V l co l t A h w l g h ntal t t f m l h lf m h p d l th t ml doubl p l b w th t m l k d p sect (C t y f N dl k A h klin exp D m t 04 213 235 1957)

ment The external muscle rings are normally so called valvular veins out of which the vascular branching seems to form as well as formation of ectasias since the large increase in a small space and asymmetrical irregularity of muscle cells appears abnormal

These changes indicate that in Rendu Osler disease dysplasia of both ground substance and vessels is primarily of venous nature The predominant factor in histopathogenesis seems to be the specific organization of the peripheral circulation including anastomoses and spreading vessels and the epithelioid cell vascular portion The development of spe

cific mechanisms that can lead to development of convolutions from tortuous dilated vessels is interpreted as the structural expression of a last unsuccessful attempt at functional adjustment of the disturbed blood circulation

Considerations on Etiology and Pathogenesis of Bateman s Senile Purpura Particularly Its Relation to Vitamin E is presented by G Mars F Gianotti and M Coronelli[6] (Milan) This condition consists of rounded irregular bluish or brick red patches (0 5 2 cm ) streaked with angiectasis localized on the extensor surfaces of the forearms back of the hands and less often on the legs feet and face The duration of evolution varies from 7 to 15 days Hematic pigment gradually degenerates until it disappears completely, often leaving a dark brown spot which lasts some months The frequent recurrences do not always occupy areas previously involved The condition is observed only in aged individuals (generally over 60) of either sex who may be ill or in good health Bateman s purpura causes no subjective symptoms locally and discovery of the lesion is purely circumstantial

Histologically senile purpura is always associated with advanced senile degeneration of the skin characterized by a very thin flat sometimes melanotic epidermis and with pronounced degeneration of collagen in the subpapillary dermis The connective fibers are often tortuous and fragmented In spaces of connective tissue degeneration, small vessels especially veins are dilated stretched and have thin walls In patches of purpura there are also extravascular hemorrhages disseminated freely in the middle and deep dermis (Fig 75) Schiff s periodic acid stain demonstrates the lack of connective tissue support of dilated vessels with a fissure between the external wall and dermal fibers The skin of exposed areas in normal persons over 60 presents an increase of elastic fibers at the expense of collagen which however are not tortuous and fragmented and are distributed uniformly between bundles of normal collagen Recently these findings were confirmed by the electron microscope

The authors studied 45 patients (4 4% of 1 014 patients of the same age range) aged 62 91 with senile purpura con

(6) P sse méd 65 2146-2149 D 25 1957

tinually for about a year No etiologic significance could be attached to type of activity sex seasonal variations or repeated slight trauma. Hematologic hematochemical and hemogenic studies showed about the same findings in normal subjects of the same age

Experimental and clinical research has shown that vitamin E deficiency may cause lesions of collagenous tissue Hence it is not improbable that changes in collagen of the

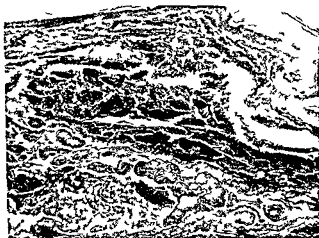


Fig 75.—Sect on of pu p pot b w g t phic p th l m ff on f blood ll betw n l ted d rm w th d g t f ll gen d la t b dl W ig rt tain d ed from 138 (C u t y f M G et l P se m d 65 2146 149 D c. 25 1957)

skin attacked by purpura belong to the same type especially since a low level of alpha tocopherol was demonstrated by the authors in patients with Bateman s purpura The vitamin deficiency however apparently is not the sole factor responsible for this pathologic manifestation The results of therapeutic trial of vitamin E were inconclusive Age and predisposition with characteristic constitution of the skin of certain areas probably contribute to the etiology and pathogenesis of the condition

► [This tudy of a commonplace physical finding in the aged is a useful contr bution. The clinical appearance is usually distinctive but may be associated w th independent hemorrhag c disease —Ed.]

**Release of Coagulation Factors** was studied with refined methods by F Koller P Baer and M Geiger (Univ of Zurich) The activity of factor IX (plasma thromboplastin component deficient in hemophilia B) in normal plasma and also in serum is less than 1% but on contact with wettable surfaces (fine quartz sand) it is activated to about 10% The intact vascular wall covered with endothelium constitutes an ideal unwettable surface but when the intima is denuded of epithelium strong activation of factor IX occurs Conversely cholesterol or calcium phosphate crystals often found in arteriosclerotic ulcers in direct contact with plasma exert no noteworthy effect on activity of factor IX This confirms pathologicoanatomic evidence (von Albertini) that the thrombus does not cling to the cholesterol or calcium deposit but to the denuded vascular intima This suggests the importance of endothelial defects in production of thrombosis

As soon as factor IX is activated conditions are present for release of coagulation precursors Platelet factor 3 is found on the surface of thrombocytes and can participate in coagulation without destruction of platelets Blood thromboplastin that converts prothrombin into thrombin is formed first A small amount of thrombin is sufficient with certain cofactors to cause platelet agglutination and destruction ( viscous metamorphosis ) This is of greatest significance both for thrombus formation and hemostasis Thrombin also functions as an enzyme in convertin fibrinogen to fibrin

Even in severe hemophilia small amounts of factor IX can be demonstrated hence coagulation is not impossible but merely prolonged The extent of decrease in concentration correlates with the clinical picture With severe hemophilia B knee hemorrhage with stiffening of the knee is frequent All degrees are observed from this classic type to mild hemophilia compatible with a normal life that is manifested only with dental extractions or surgical operations (7% factor IX in serum) Between these two extremes

(7) Acta ha m t 18 33 41 1957

stands hemophilia B (factor IX content 2-4%) the geneal ogy of which has been thoroughly studied In transmittors the content of factor IX is normal (around 100%)

In prophylaxis and therapy of thrombosis with Dicu marol[8] and its derivatives factor IX decreases but usually remains over 10% With overdosage and long administra tion occasionally the level of factor IX approaches that of hemophilia B Unfortunately this coagulation factor is not determined by the Quick test which explains why bleeding sometimes occurs with optimal Quick determinations

Similar considerations apply in hemophilia A character ized by lack of coagulation factor VIII except that factor IX must first be activated while factor VIII is present and ac tive in plasma Both factors participate in formation of blood thromboplastin and therefore indirectly of thrombin If thrombin formation is almost nil as in severe classic he mophilia then viscous metamorphosis of blood platelets and fibrin formation will be implicated Since platelet formation is linked closely with clot retraction the latter yields an approximate measure of thrombocyte reaction Retraction is definitely delayed in classic hemophilia but in the mild type is normal Severe hemophilia is not purely a disturbance of coagulation but is accompanied by the hemostatic dysfunc tion of the platelets Afibrinogenemia despite complete in coagulability of the blood displays a less severe hemorrhagic diathesis than classic hemophilia Thrombin formation and platelet reaction (viscous metamorphosis) are undisturbed *hence afibrinogenemia represents a pure coagulopathy*

Thrombin formation can also be initiated by tissue throm boplastin which uses for its formation especially on activa tion with calcium only factors V and VII both of which are present in active form in plasma With this thromboplastin activation precursors play no role as soon as tissue fluid comes in contact with blood coagulation begins In injuries i e with hemostasis tissue thromboplastin undoubtedly plays a significant part in thrombogenesis it remains in the background With a dissecting aneurysm a lesion of the intima or desquamation of the endothelium some tissue thromboplastin may well reach the circulation and partici pate in thrombus formation but thromboplastin from the blood itself (with activation of factor IX) is probably much more important

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(7) Acta h emat. 18 33-41 1957

Alton suspended in saline and stored at −20 C Normal plasma is used for controls

The plasma to be tested is diluted with Veronal® buffer at pH 7 35 in a ratio of 1 9 and 0 5 ml diluted plasma and 0 5 ml platelet substitute are mixed in a test tube in a water bath at 37 C Then 0 5 ml of previously warmed calcium chloride (0 025 M) is rapidly added and a stop watch started At 1 minute intervals successive 0 1 ml samples are removed from the mixture and added with 0 1 ml calcium chloride solution to one of a series of test tubes containing 0 1 ml normal plasma previously placed in the water bath The clotting times of the normal plasma are then recorded A wooden applicator stick is placed in the incubation mixture soon after addition of calcium chloride solution The clot which forms usually within 2 minutes adheres to the stick and can be easily removed.

In patients with hemophilia plasma concentrations of antihemophilic globulin were also determined The rapid screening test described is as sensitive as the orthodox thromboplastin generation test in demonstrating deficiencies of thromboplastin precursor substances The test is not sensitive to disorders other than those induced by deficiencies in thromboplastin generation It is reliable as a screening test for thromboplastin deficiency in routine investigation of suspected coagulation disorders

**Deficiency of Antihemophilic Globulin in Heterozygous Hemophilic Females** Hemophilia is a hemorrhagic disease mostly affecting men and inherited as a sex linked recessive Plasma is deficient in a specific clotting factor called antihemophilic globulin All daughters of a hemophilic man are transmitters whereas all sons are healthy In the family of a transmitter female half the sons may be hemophilic and half the daughters transmitters The homozygous hemophilic state is possible in the daughter of a hemophilic man and a transmitter woman

A S Douglas and I A Cook[9] (Glasgow) studied 2 heterozygous transmitter hemophilic females who had significant hemorrhagic tendencies due to deficiency of antihemophilic globulin revealed by thromboplastin generation and prothrombin consumption tests Their antihemophilic globulin levels were about 20% of normal thus resembling those of mild hemophilia They were daughters of a patient with hemophilia whose wife s ancestors were unaffected The affected male members of the father s family had mild hemophilia

(9) Lancet 616-619 S pt 8 1957

The authors conclude that in release of blood coagulation two mechanisms play a role If tissue thromboplastin is mixed with blood because of trauma the coagulation process begins immediately This precursor plays the decisive role in hemostasis With intravascular coagulation i e thrombosis thrômboplastin of blood itself is principally involved It requires for its formation besides platelets (which must not be destroyed) and calcium a series of plasma factors among them factor IX (antihemophilia B factor) which is normally inactive in plasma but is activated by contact with wettable surfaces (quartz crystal glass wool and also vascular intima denuded of endothelium) This sheds light on the significance of endothelial lesions in production of thrombosis Destruction of platelets indispensable for hemostasis and also for thrombogenesis constitutes a result not the cause of blood coagulation since it can occur only in the presence of thrombin and certain cofactors

**Rapid Screening Test for Disorders of Thromboplastin Generation** is described by N D Hicks and W R Pitney[8] (Postgrad Med School London) The thromboplastin generation test is sensitive in detecting abnormalities in early stages of blood coagulation Abnormalities can be detected in patients with hemophilia or Christmas disease In mild hemophilia other clotting tests may be normal The investigation of a suspected hemorrhagic disorder is seldom complete until mild hemophilia has been excluded The screening test described cannot be used to the exclusion of the thromboplastin generation test but it can be useful as an exclusion test eliminating blood samples in which further investigation is unnecessary Diluted whole plasma is recalcified in the presence of a platelet substitute and the thromboplastin generated is tested by adding subsamples of the incubation mixture and excess calcium to normal citrated plasma which has been centrifuged at high speeds

METHODS —Venous blood is collected in a syringe through a 19 gauge needle with avoidance of undue suction or frothing of the blood in the syringe Nine parts blood are mixed with 1 part of 3 8% (weight/volume) trisodium citrate and the plasma is separated by centrifugation at 3 000 rpm for 10 minutes The plasma is kept at 4 C until tested within 6 hours of collection A chloroform extract of acetone-dried human brain is prepared as described by Bell and

(8) B t J H m t 3 27 237 1957

Alton suspended in saline and stored at −20 C Normal plasma is used for controls

The plasma to be tested is diluted with Veronal® buffer at pH 7.35 in a ratio of 1 9 and 0 5 ml diluted plasma and 0 5 ml platelet substitute are mixed in a test tube in a water bath at 37 C Then 0 5 ml of previously warmed calcium chloride (0 025 M) is rapidly added and a stop watch started At 1 minute intervals successive 0 1 ml samples are removed from the mixture and added with 0 1 ml calcium chloride solution to one of a series of test tubes containing 0 1 ml normal plasma previously placed in the water bath The clotting times of the normal plasma are then recorded A wooden applicator stick is placed in the incubation mixture soon after addition of calcium chloride solution The clot which forms usually within 2 minutes adheres to the stick and can be easily removed

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(9) Lancet 2 616-619 Sept. 8 1957

The female bleeders in hemophilic families cited in published reports probably represent homozygous hemophiliacs One such patient when retested had a pure deficiency of antihemophilic globulin The 2 sisters in the present report were considered heterozygous but still had a significant hemorrhagic tendency

The information about hemostasis in female transmitters of hemophilia is conflicting In a careful review of 27 carriers only 1 had levels of antihemophilic globulin definitely lower than normal In another group of 23 known carriers only 3 had abnormal prothrombin consumption tests Thus the available experience with female transmitters suggests that only rarely can a significant defect be demonstrated

**Possible New Thromboplastin Deficiency Occurring in Five Siblings** is reported by Anna Marie Chirico and Arthur E McElfresh[1] (Temple Univ ) All had excessive bleeding after surgery The parents were normal Clotting times and prothrombin consumption tests were normal in all the patients and the defect was unknown until the thromboplastin generation test was performed The deficient factor is present in normal serum It differs from plasma thromboplastin component plasma thromboplastin antecedent Hageman factor and Stuart factor by cross correction studies and does not have the properties of Duckert s factor X Bleeding times and prothrombin times were normal in the patients

The hemorrhagic tendency is mild compared to classic hemophilia The defect is only demonstrable by the thromboplastin generation test The responsible factor in the serum is absorbed by barium sulfate and is labile on heating to 60 C for 3 minutes It is precipitated from serum by ammonium sulfate It is stable when stored at room temperature for 12 days and not reduced by 11 days of Dicumarol® therapy

The inheritance of this defect present in 5 of 6 siblings is not clear It was associated with bleeding after tonsillectomy in 2 patients and after extraction of teeth in 2 others In 3 of the 4 affected sisters it was associated with severe vaginal hemorrhage and abnormal menses This defect appears to be unique and has not been previously described It was named the Car factor an abbreviation of the family name of the persons in whom it has been found to be deficient

(1) Blood 12 933 941 October 1957

**Inherited Autosomal Hemorrhagic Diathesis with Anti hemophilic Globulin (AHG) Deficiency and Prolonged Bleeding Time** Inga Marie Nilsson Margareta Blomback and Irene von Francken studied 6 female and 3 male patients from 6 different families with a hemorrhagic disorder characterized by deficiency of antihemophilic globulin and prolonged bleeding time

The most common bleeding manifestations were ready bruising epistaxis bleeding from the gums and uterus and prolonged bleeding after small lacerations and surgery Three patients had joint bleeding but no deformities Only 1 had petechiae Coagulation was moderately prolonged bleeding time was prolonged platelet counts prothrombin and fibrinogen were normal The plasma levels of antihemophilic globulin were 1 10% of normal in 6 patients and 10 15% of normal in the other 3 Human plasma fraction I O prepared from Cohn s fraction I and containing anti hemophilic globulin corrected the clotting defect of each patient in vitro In 3 treated with this preparation intravenously bleeding promptly stopped A deficiency of anti hemophilic globulin was thus considered the cause

However the effect of fraction I O on the bleeding time did not parallel the effect on the coagulation defect and in 2 cases the bleeding time could be influenced by giving a fraction of I O which did not contain antihemophilic globulin activity Most likely the prolonged bleeding time in this syndrome is caused by a deficiency of a vascular factor which is present in fraction I O and not identical with antihemophilic globulin or fibrinogen

The disease is inherited autosomal and dominant but with varying degrees of expressivity It is not sex linked The antihemophilic globulin values of affected subjects in a family showed a wide variation from 2 to 62% Only those with less than 20% had marked bleeding

The bleeding disorder in these 9 patients apparently is a special type of hemorrhagic diathesis similar to that reported by others variously as vascular hemophilia or pseudo hemophilia B It differs from von Willebrand s thrombopathy in that the platelets show normal activity in the thromboplastin generation test It differs from classic hemophilia A in that the bleeding time is also prolonged and

(2) Act m d. sca d 159 35 57 1957

inheritance is not sex linked The prolonged bleeding and coagulation times are apparently due to the lack of a plasma factor present in fraction I O but distinct from fibrinogen and antihemophilic globulin Contrary to previous opinions the condition is not due to an anatomically demonstrable disturbance in the capillary wall

Deficiency in Hageman Factor (a syndrome first described by Ratnoff and Colopy in 1955) was discovered in a case reported by M J Larrieu J P Soulier and Y Culot[3] (Paris)

Woman 50 had a coagulation time of 60 minutes discovered during a preoperative examination She had had no hemorrhages and had undergone appendectomy and several dental extractions without excessive bleeding She had only a slight ecchymotic tendency There was no family history of hemorrhagic disorders The patient was an only child and had no children Clotting time capillary resistance and platelet count were normal Total coagulation time was moderately but definitely prolonged at 37 C it was 17 21 minutes at about 25 C it extended to 31 minutes Recalcification time was definitely prolonged also the heparin tolerance test. Consumption of prothrombin confirmed existence of a significant disturbance of hemostasis Quick test and differential determinations of prothrombin proconvertin and proaccelerin were normal Cephalin time was greatly prolonged indicating a plasma disorder There was no circulating anticoagulant. The Biggs and Douglas test showed normal platelet function Conversely thromboplastin formation normal with patient s serum alone or plasma alone was practically nil if both plasma and serum were used There was no lack of antihemophilic factor A or B confirmed by determinations of these factors but of a third prothromboplastic factor in plasma with characteristics analogous to those of PTA or Hageman factor A small quantity of plasma injected in vivo sufficed to restore normal hemostasis The disturbance of coagulation was not corrected by Hageman plasma in cross tests on total blood and plasma preparations made in the authors laboratory and in Cleveland by Dr Ratnoff

Contrary to observations by Ratnoff the plasma disturbance was not corrected by plasma from 2 patients previously diagnosed as having PTA deficiency This poses a complex problem as to the relation between the PTA and Hageman factors A relationship is likely but it remains to be demonstrated conclusively

Nature of Hemorrhagic Disorder Accompanying Hemolytic Transfusion Reactions in Man Sudden onset of unexplained bleeding may be the first sign of a hemolytic transfusion reaction especially in patients under general anesthesia Hypofibrinogenemia hypoprothrombinemia and thrombocytopenia have been observed in some instances but the nature of the hemorrhagic disorder remains unsolved

(3) Sang 28 152 159 1957

Julius R Krevans Dudley P Jackson C Lockard Conley and Robert C Hartmann[4] (Johns Hopkins Univ ) report on 2 patients who showed abnormal bleeding after inadvertent administration of 500 ml incompatible whole blood In 1 patient onset of unexplained bleeding during surgery was the first evidence of a transfusion reaction bleeding was severe and additional compatible blood transfusions were given In both patients the hemostatic defects were hypofibrinogenemia hypoprothrombinemia and thrombocytopenia and there was no evidence of increased fibrinolytic activity In 1 accelerin (factor V) activity was reduced and there was transient evidence of a low titered circulating anticoagulant In both the fibrinogen and prothrombin rapidly returned to normal but thrombocytopenia persisted for several days

The pathogenesis of the coagulation defects is uncertain When smaller amounts of incompatible blood are transfused hemorrhage does not develop The most likely etiology is intravascular clotting long known to be initiated by the experimental injection of lysed red cell stromas but not of hemoglobin

The proper management of the patient with a hemolytic transfusion reaction demands recognition that in addition to shock and renal damage a potentially fatal hemorrhagic diathesis may occur The danger of hemorrhage is present immediately after transfusion and persists for several days This is especially important in anesthetized patients undergoing surgery in whom uncontrollable bleeding from the operative site may be the first sign of a hemolytic transfusion reaction When serious bleeding occurs the only complete replacement therapy is compatible fresh whole blood Intravenous infusions of fibrinogen may also be helpful This regimen corrects hypofibrinogenemia hypoprothrombinemia thrombocytopenia and deficiency of other clotting factors

**Bleeding Diathesis Associated with Circulating Fibrinolysin Report of Three Cases** is presented by B G Firkin C S H Reed and C R B Blackburn[5] (Sydney) Plasma contains a factor termed profibrinolysin (plasminogen) which may be activated to form the proteolytic enzyme

(4) Blood 12 834 843 S pt mbe 1957
(5) B t. J II m t. 3 193 201 1957

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(3) Sang 28 152 159 1957

in which the cause is undetermined The diagnosis is con firmed by collecting 1 ml whole blood in each of two tubes incubating at 37 C and examining the clot after 24 and 48 hours Complete fibrinolysis is recorded if the clot is entirely dissolved Partial fibrinolysis denotes a clot not totally dis solved but smaller and more fragile than normal

To treat acute episodes blood loss should be replaced with fresh whole blood If fibrinogen is reduced it should be re placed Human serum albumin in 25 Gm units with or with out ACTH or cortisone may increase the antifibrinolytic activity of the patient s blood

**Studies on Fibrinolysin Using Clinically Practical Method of Quantitative Determination** Most technics are fairly complicated and unsuitable for the routine clinical labora tory The one described by Edward Adelson and William H Roeder[6] (Walter Reed Army Med Center) is quantitative and suitable for any clinical laboratory It employs normal plasma as substrate and defibrinated plasma as test material

METHOD—For defibrinogenation of plasma heat it for 3 minutes at 56 C centrifuge for 5 minutes at 1 000 rpm add 100 units of thrombin to each milliliter of supernatant plasma and squeeze out the clot To activate profibrinolysin add 0 1 ml chloroform plus 0 04 ml of 0 5 M CaCl to each milliliter of plasma incubate at 37 C for 30 minutes centrifuge and remove chloroform layer The residual serum is kept uncovered overnight in the refrigerator and is ready for use the next morning Measure fibrin levels by tyrosine determi nation using Folin Ciocalteu phenol reagent Dilute 1 ml plasma to 25 ml with saline or distilled water plus 100 units of thrombin and incubate the resultant clot at 37 C for various periods To separate fibrin pass through a glass wool filter squeeze out and wash re peatedly with 0 9% saline Measure fibrin content by the routine colorimetric technic of tyrosine determination

To measure fibrinolysin heat fresh normal and test plasmas to 56 C for 3 minutes cool centrifuge and save supernatants Add 1 ml normal plasma to each of 4 tubes labeled A B C and D To A and B add 1 ml defibrinogenated normal plasma to C and D add 1 ml de fibrinogenated test plasma Bring total volume in each tube to 24 ml with saline Incubate at 37 C Add 1 ml thrombin (100 units/ml ) to each tube After 15 minutes incubation take tubes A and C from water bath filter through glass wool wash glass wool clot mixture repeatedly with distilled water and squeeze out excess moisture Do tyrosine determinations on both clots After 24 hours incubation repeat same steps on tubes B and D Final results are expressed in terms of percentage loss of fibrin

If substrate fibrinogen is low enough normal fibrinolysin will cause complete clot lysis Thus fibrinogenopenia may

(6) J Cl P th 11 82 86 J y 1958

fibrinolysin (plasmin) It also contains the precursor of an activator of profibrinolysin termed profibrinolysin proactivator (plasminogen proactivator) which itself may be activated to form the activator of profibrinolysin Tissue contains a factor termed fibrinokinase which activates profibrinolysin to fibrinolysin Similar activity has been found in normal urine milk and tears Certain bacterial products activate the blood fibrinolytic system Normal circulating human plasma contains a low level of fibrinolysin held inactive by loose combination with antifibrinolysin (antiplasmin)

Overt bleeding associated with circulating fibrinolysin is well documented It has been reported after shock thoracic and pancreatic surgery disseminated carcinomatosis cirrhosis of the liver radiation injury transfusion reactions extensive burns and afibrinogenemia associated with a retained dead fetus In the 3 cases reported the bleeding manifestations were sufficiently characteristic to enable the correct diagnosis to be suspected clinically

CASE 1—Man 22 had bleeding episodes after surgical and dental operations No underlying disease was found Fibrinolytic activity of the plasma was less than in the other 2 cases since clots did not lyse completely The Macfarlane dilution test showed fibrinolysin activity against the patient s and normal clotted plasma

CASE 2—Man 61 had bleeding after a dental extraction and hematoma after heavy manual labor The spleen was enlarged and hard The peripheral blood count was abnormal and megakaryocytes were increased in the bone marrow Complete fibrinolysis was observed The fibrinogen content was not determined but the size and consistency of a whole blood clot 1 hour after withdrawal suggested that fibrinogen was diminished

CASE 3—Man 39 had bled on 5 occasions over the previous 15 years for 12 24 hours after tooth extractions Later he had a severe occipital headache and became stuporous The cerebrospinal fluid was heavily blood stained Complete fibrinolysis was present as was thrombocytopenia which contributed to the bleeding

The syndrome can be suspected if onset of bleeding after trauma is delayed In hemophilia Christmas disease and other primary coagulation disorders bleeding is intense 1 2 hours after trauma or operation In patients with a circulating fibrinolysin the bleeding is apparent 1 8 days after injury

A bleeding diathesis associated with a circulating fibrinolysin is probably more common than has been realized Its presence should be suspected in all secondary hemorrhage

in which the cause is undetermined The diagnosis is confirmed by collecting 1 ml whole blood in each of two tubes incubating at 37 C and examining the clot after 24 and 48 hours Complete fibrinolysis is recorded if the clot is entirely dissolved Partial fibrinolysis denotes a clot not totally dissolved but smaller and more fragile than normal

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(6) J Cl P th 11 82 86 J y 1958

be mistaken for fibrinolysis unless the fibrin present in the test system is controlled Methods for preparing pure fibrinogen do not remove the fibrinolysin, so there is no ad vantage in using purified materials in the test

The mere demonstration of fibrinolysis is without patho logic significance The degree of lysis is the important fac tor Adding a definite amount of normal plasma after re moving the native fibrinogen in the test material controls the amount of substrate and eliminates any variation which might erroneously be attributed to differences in fibrinolysin content

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## DRUG ASSOCIATED BLOOD DYSCRASIAS

This section continues the attempt made for the first time in the 1956 57 YEAR BOOK to bring together references to a majority of current case reports in the world literature con cerning the above topic As previously the reader is urged to weigh the evidence in the light of the therapeutic prob lems of particular patients and to consider that in some re ported instances of an association a causal relation has not been established Obviously the employment of any of the drugs referred to below is justified by appropriate clinical circumstances —Ed

*Aplastic anemia or pancytopenia*

Albahary C Dubrisay J Guerin Obstinate pancytopenia due to lindane (isomer of herachlorocyclohexane) Arch mal profess Paris 18 687 691 November December 1957

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Gueron B Lacks S and Reilblat I Acute bone marrow insufficiency subsequent to infection or administration of pyramidon Harefuah Tel Aviv 52 260 May 5 1957

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# THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

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TINSLEY R. HARRISON M D

# PART IV

# THE HEART AND BLOOD VESSELS AND THE KIDNEY

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## CONGENITAL HEART DISEASE AND CARDIAC SURGERY

**Prognosis of Isolated Ventricular Septal Defects** was re evaluated by E Mannheimer D Ikkos and B Jonsson[1] (Karolinska Hosp Stockholm) in 72 patients aged 3 months to 20 years Each had a complete clinical examination includ ing phonocardiography ECG s x rays and cardiac catheteri zation Angiocardiography was performed in some

In the most severe cases definite cardiac symptoms were present in infancy Health often improved after the 1st year of life Physical underdevelopment was infrequent and cya nosis rare Fatigue and dyspnea were observed in severe cases but most were without symptoms

The patients could be divided into five groups and the physical signs within each group was surprisingly charac teristic In group Ia the systolic murmur was the only sign of septal defect It was fairly high pitched and the 2d sound was normally split The murmur was often localized to a dis tinct area at the 3d-4th left interspaces and poorly trans mitted Patients in group Ib had normal pressures and sig nificant left to right shunts The systolic murmur was often more intense and extended throughout systole Group II was characterized by moderately raised right ventricular pres sure a heaving cardiac impulse a harsh systolic murmur and the 2d sound was more accentuated and only slightly split In group IIIa with equilibrated pressures and left to right shunts the systolic murmur was loud with a marked thrill the impulse was heaving the precordium bulged and the 2d sound was much accentuated but not clearly split In group IIIb with equilibrated pressures and mixed shunts the systolic murmur was faint but the pulmonic 2d sound was

(1) B t. H t J 19 333 344 J ly 1957

this inverted V the moderator band extends as a bridge from the septum to the anterior papillary muscle

A characteristic pattern of rSr was demonstrated in at least one lead when multiple leads were obtained from the right side of the chest in 49 of 50 normal children studied This pattern results from three vector forces (1) depolarization of the interventricular septum and portions of the right ventricle resulting in positivity to the right and an upright deflection in right precordial leads (2) simultaneous depolarization of the left and right ventricles with a resultant force vector directed down and toward the left causing a downward deflection or S wave and (3) late depolarization of the area of the right ventricular outflow tract with the resultant vector toward the right causing a terminal positive deflection or r wave

Direct epicardial leads during surgery on patient with atrial septal defects revealed the rSR or rSR s patterns only from the right ventricular outflow tract with RS patterns from the midright ventricle Follow up ECG s in patients with valvular pulmonary stenosis after surgery demonstrated gradual transition of obvious right ventricular hypertrophy patterns to rSR and finally rSr This further substantiates the concept that hypertrophy of the right ventricular outflow tract explains this ECG pattern This pattern can be precisely duplicated by incomplete right bundle branch block

In certain congenital and acquired lesions predominantly atrial septal defects an rSR pattern with a QRS duration of 0 08 0 1 second is due to hypertrophy of the right ventricular outflow tract rather than to incomplete right bundle branch block

**Differentiation of Tetralogy of Fallot from Severe Pulmonary Stenosis with Intact Ventricular Septum and Right to Left Interatrial Shunt** Correct diagnosis is imperative because surgical treatment of the two conditions is different An anastomosis between the systemic and pulmonary arteries is contraindicated in the second Louis Vogelpoel Velva Schrire Maurice Nellen and Robert H Goetz[3] (Univ of Cape Town) review findings in 14 cases of severe pulmonary stenosis with intact ventricular septum and 48 cases of the tetralogy

(3) A g l gy 8 15 247 J e, 1957

markedly accentuated often palpable, though not split A few patients had no murmurs A parasternal lift along the left sternal border indicated right ventricular hypertrophy

The clinical findings allowed differentiation on the basis of the pulmonic 2d sound In mild cases the sound was normally split In pulmonary hypertension the 2d sound was accentuated and pure In patients with normal right ventricular pressure the x ray appearance was normal With increased flow and right ventricular pressure the heart was enlarged pulsations increased in the pulmonary artery and the left atrium dilated Left atrial enlargement indicated the presence of a shunt below the level of the atria With increased pressure the right ventricle was enlarged and bulged against the thoracic wall

Patients with ventricular septal defects but without pronounced hemodynamic changes had a loud systolic murmur over the 3d left interspace a normally split 2d sound and a normal ECG or slight left ventricular hypertrophy Severe cases were characterized by a highly accentuated 2d sound not split and a loud murmur throughout systole or sometimes a faint murmur or none the ECG showed combined left and right ventricular hypertrophy and some showed signs of atrial enlargement

**Hypertrophy of Right Ventricular Outflow Tract Concept of ECG Findings in Atrial Septal Defect.** The rSr pattern in the right precordial leads in normal children and the rSR complex with a total QRS interval of 0 08-0 1 second in congenital and acquired cardiac defects cannot be satisfactorily explained as incomplete right bundle branch block S Gilbert Blount Jr E Addis Munyan Jr and Murray S Hoffman[2] (Univ of Colorado) believe this pattern is due to hypertrophy of the outflow tract of the right ventricle and is not the result of disturbed ventricular conduction

Anatomically the outflow tract of the right ventricle (or infundibulum) is bounded anteriorly and to the right by the free wall of the right ventricle Posteriorly and to the left lies the interventricular septum behind which is the outflow tract of the left ventricle The pulmonary valve lies superiorly A triangular ridge of muscle the crista supraventricularis shaped like an inverted V extends from the anterior free wall to the interventricular septum Below the septal insertion of

(2) Am J Med. 22 784 790 M y 1957

sabot shaped the aorta is wide and may be right sided Pulmonary oligemia and right ventricular hypertrophy are common to both lesions

Cardiac catheterization and angiocardiography provide special anatomic information and occasionally may be essential for diagnosis Demonstration of infundibular stenosis favors diagnosis of the tetralogy Passage of a catheter from *the right ventricle to the aorta is pathognomonic Selective* angiocardiography is useful in some patients In severe pulmonary stenosis with intact ventricular septum marked early opacification of the left atrium and left ventricle prematurely opacifies the aorta In the tetralogy the aorta is filled from the right ventricle

The fundamental difference in the dynamics of the two conditions are responsible for the differentiating features In the tetralogy though stenosis is always severe the ventricular septal defect and overriding aorta act as a safety valve the pressure in the right ventricle cannot exceed that in the left or in the aorta consequently the right ventricle is seldom under stress and rarely fails In pulmonary stenosis with intact ventricular septum the right ventricular pressure must rise often to great heights to maintain circulation The right atrial pressure also rises leading to the right to left atrial shunt and thus to central cyanosis

**Clinical Physiologic and Pathologic Findings in Mitral Stenosis and Regurgitation** The clinical ECG and x ray findings in 79 patients operated on for mitral stenosis or incompetence were critically reviewed by Lawson McDonald *James B Dealy Jr Murray Rabinowitz and Lewis Dexter*[4] (Harvard Med School) Forty four of these had preoperative cardiac catheterization determination of cardiac output and an accurate operative estimate of the mitral valve area

In the spectrum of mitral valve disease from pure stenosis to slight and then gross incompetence one or the other lesion usually predominates functionally Attempts to quantitate the degree of regurgitation have proved unsuccessful The height of the v wave in the pulmonary capillary catheter tracing and the systolic expansion of the left atrium have proved unreliable Electrokymography roentgenkymography radiokymography esophageal pulse wave tracings ballistocardiography records of pulse wave from the

(4) Med 36 237 280 S pt mbe 1957

In general central cyanosis begins earlier in the tetralogy of Fallot and was present by age 5 in all cases Only 6 of the 14 patients with severe pulmonary stenosis and intact ventricular septum were cyanotic by age 5 A history of squatting was noted in 70% of patients with the tetralogy and in only 36% of those with the latter condition but this was of no differential value in a given case

Pulsation of the jugular vein was a major differentiating point The severity of pulmonary stenosis in patients with an intact ventricular septum could be correlated with the size of the *a* wave An *a* wave of about 5 mm Hg was associated with ventricular pressures between 51 and 100 mm Hg a 10 mm Hg *a* wave with pressures of 125 175 mm Hg A giant *a* wave was never observed in the tetralogy of Fallot The absence of a visible dominant *a* wave does not exclude severe pulmonary stenosis with intact ventricular septum

In both conditions the apex beat was almost always within normal limits and difficult to locate In no case was a thrusting localized left ventricular impulse felt A right ventricular systolic lift between the sternum and midclavicular line was never marked in the tetralogy but was present in most cases of severe stenosis with intact ventricular septum

The most important and constant clinical differentiating features are found by auscultation In severe pulmonary stenosis with intact ventricular septum the systolic murmur at the site of maximal intensity is so prolonged it extends beyond and obscures the normal aortic component of the widely split second sound It stops however before the markedly delayed diminutive pulmonary component which may or may not be audible In the tetralogy the systolic murmur starts soon after the first sound reaches maximal intensity by midsystole and then diminishes markedly usually ending before the single loud often palpable aortic component of the second sound

An ECG pattern of right atrial and right ventricular hypertrophy is common to both conditions but that of extreme hypertrophy favors diagnosis of an intact ventricular septum In most patients the diagnosis can be suggested by radiology alone In cases of intact ventricular septum the heart is usually larger and poststenotic dilatation of the pulmonary arteries is marked In the tetralogy the heart is often

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(4) M d n 36 237 280 S pt mb 1957

left atrium pressure curves from suprasternal puncture venous angiocardiography or the injection of contrast medium into the left atrium may demonstrate qualitatively the presence of mitral incompetence but not the degree

Three grades of forward mitral valve area less than 0 8 cm² 0 9 1 6 cm² and 1 7 cm² or larger appear to correspond to three hemodynamic divisions of mitral valve disease in severely handicapped patients stenosis mixed lesions and incompetence The normal valve is about 4 cm A severe degree of mitral stenosis and incompetence cannot co exist if severe one must predominate

The high pulmonary vascular resistances found in mitral stenosis rarely occur in mitral incompetence though resistance may be increased Cardiac indexes are reduced in mitral disease severe enough to produce marked symptoms whether stenosis or incompetence predominates Most patients with forward mitral valve areas of less than 0 8 cm i e pure stenosis had right ventricular hypertrophy by ECG and right ventricular dominance by x ray Most patients with valve areas greater than 1 7 cm² i e pure incompetence had left ventricular hypertrophy and enlargement

Clinical history reveals no features which can distinguish predominant stenosis from incompetence A pulse which was small in quality and quantity was usual in patients with pure mitral stenosis and became less so as incompetence intervened The apical 1st heart sound was almost always accentuated or markedly accentuated in mitral stenosis and normal or diminished in incompetence but there were exceptions An opening snap of the mitral valve was usual in patients with the smallest valves

In a patient who is handicapped by dyspnea or fatigue and in whom mitral disease is the responsible valvular defect the following appear to be of value in deciding whether the predominant functional lesion is mitral stenosis or incompetence (1) A left ventricular type of apex beat excludes stenosis but a right ventricular apex beat may sometimes occur in incompetence if the pulmonary vascular resistance is considerably raised Left ventricular hypertrophy as revealed by the ECG and left ventricular dominance by x rays logically al o exclude stenosis but right ventricular hypertrophy by ECG or right ventricular dominance by x rays may occur in incompetence if the pulmonary vascular resistance is raised

considerably but this is rare (2) An accentuated 1st heart sound or opening snap indicates stenosis In incompetence the mitral systolic murmur is almost always impressive (3) Demonstration of a significant pressure gradient without a significant regurgitant flow across the mitral valve is the only sure way to differentiate mitral stenosis from incompetence Attribution of incapacitating symptoms to mitral stenosis should be reconsidered if the pulmonary vascular resistance is normal Symptoms attributed to mitral incompetence should similarly be reviewed if the cardiac index is normal since it should be significantly decreased

Clinical examination of patients with mitral disease will most often differentiate mitral stenosis from incompetence The clinical signs with the other information described seldom leave doubt as to which lesion is dominant

**Quantitation of Backflow in Patients with Aortic Insufficiency Using an Indicator Technic** Homer R Warner and Alan F Toronto[5] (Salt Lake City) describe a method which permits estimation of the time course of backflow velocity in the descending aorta of patients with insufficiency of the aortic valve

METHOD—An arterial catheter is advanced into the thoracic aorta through an indwelling thin walled 18-gauge needle in the right femoral artery until its tip lies near the origin of the left subclavian artery The proximal end is connected to an injection device The R wave of the ECG is amplified and used to initiate the injection of 0 15 0 62 ml dye solution (Evans blue) The concentration of dye is continuously and simultaneously detected in blood from the left radial and left femoral arteries by cuvet oximeters and is recorded photographically on kymograph paper If the maximum deflection from the radial artery is larger than from the femoral the catheter tip has entered the left subclavian artery The catheter is then withdrawn and further injections made until the two deflections are equal At this point the catheter tip must lie at or near the origin of the left subclavian artery

As the catheter is withdrawn by increments of 3 5 cm injections are made at each increment at specified times in the heart cycle Then the ratio of area under the radial curve to area under the femoral curve (denoted by symbol $R$) can be obtained as a function of time and distance

The logarithm of $R$ is plotted as a function of the distance in centimeters that the catheter is withdrawn In most cases of aortic insufficiency the slope of such a plot can be represented by a constant ($k$) for values of $R$ between 1 0 and 0 1

(5) C 1 t n R 6 29 34 J ry 1958

In the absence of aortic insufficiency $k$ is greater than 10 and in patients with clinically severe aortic insufficiency and dogs with one leaflet of the aortic valve incised to the ring $k$ is less than 0 2

Quantitation of the severity of the hemodynamic defect in a patient with aortic insufficiency may be accomplished simply by determining $k$ the fractional decay of $R$ per centimeter at a delay of 0 4 second When $k$ is 0 2 $b$ (distance from origin of the subclavian artery) will be 11 cm for $R$ of 0 1 when $k$ is 0 1 $b$ will be 23 cm for $R$ of 0 1 If it is assumed that the average cross sectional area of the aorta in such a case is 4 0 sq cm the back volume per stroke from this section of the arterial bed alone would be 92 ml

► [The various surgical attacks on aortic insufficiency still leave much to be desired. However there is much reason to hope and some to believe, that this situation will be changed within the near future If this should happen the quantitation of aortic insufficiency will become a matter of great practical importance Aside from the technic mentioned by the authors another method which looks hopeful is the use angiograms following injection of the dye into the root of the aorta. The study of differential pressure pulses obtained from the root of the aorta offers another approach to this problem —Ed ]◄

**Selection of Patients for Mitral and Aortic Valvuloplasty** Laurence B Ellis Walter H Abelmann and Dwight E Harken[6] (Boston) consider that patients with the murmur of mitral stenosis but without symptoms (group I) do not require surgery With moderate but nonprogressive symptoms (group II) the operation is elective depending on the social economic and psychologic situation Medical care and observation are indicated before surgery is advised Patients disabled by progressive symptoms chiefly dyspnea but not yet complete cardiac invalids (group III) need the operation urgently Operative risk is low results are excellent and prognosis without surgery is poor Group IV patients are cardiac invalids condemned to complete inactivity under medical treatment with relatively short life expectancy In these patients the operative risk remains high but results are surprisingly good and operation should be offered Had they been operated on as group III the risk would have been lower by a factor of about 1 30

The mortality rate of mitral valvuloplasty in the first consecutive 1 000 patients has steadily fallen so that risk in groups II and III now is less than 1% but in group IV remains at about 20% In groups III and IV 78% and 62%

(6) Circulation 15 924 935 June 1957

respectively improved significantly and maintained the improvement for 5 years of follow up Improvement was due to the operation itself not to the psychologic effect of the procedure nor to better medical care as proved by improvement *in the circulatory hemodynamics The results in* valvuloplasty have been striking when compared with those to be expected from medical management of groups III and IV patients

Before surgery is considered symptoms must be disabling or progressive Careful history may have to be taken from family and friends to evaluate properly the story from patients who minimize or exaggerate symptoms Right ventricular hypertrophy by ECG or enlargement of the right ventricle and pulmonary artery by fluoroscopy suggests significant stenosis Cardiac catheterization may be needed to resolve difficult problems

In pure mitral stenosis without other cardiac or pulmonary disease right heart catheterization may be of clinical value However when clinical signs of stenosis are equivocal particularly when mitral regurgitation also is suspected or when aortic valve disease or myocardial failure is present the method of choice is percutaneous catheterization of the left heart There is no absolute method for differentiating stenosis from insufficiency clinically Predominant mitral insufficiency contraindicates the conventional operation for stenosis When stenosis predominates and is at least moderate in degree valvuloplasty will improve more than half the patients even though insufficiency is present

*Peripheral embolization is a hazard to patients with mitral* stenosis particularly if fibrillating Medical treatment is unsatisfactory in preventing emboli Postoperatively likelihood of an embolus is slight presumably because stasis is reduced in the atrium Operation may be recommended in patients who have had previous emboli

Rheumatic activity is difficult to diagnose in these patients If flagrant rheumatic activity is obvious surgery should be postponed When doubt exists as to rheumatic activity and obstructive symptoms are obvious operation is worth while

In many instances the extent to which myocardial failure *contributes to symptoms is difficult to establish* Acute episodes of congestion or an unusually large heart suggest failure of the myocardium Left ventricular diastolic pressure

can be measured by left sided cardiac catheterization which thus can directly measure left ventricular competence

When significant aortic stenosis coexists with significant mitral stenosis both should be treated Significant aortic regurgitation contraindicates mitral valvuloplasty but does not often accompany pure severe mitral stenosis The diastolic murmur frequently heard along the left sternal border in patients with mitral stenosis often is due to pulmonic rather than aortic insufficiency Functional tricuspid insufficiency especially associated with atrial fibrillation is common in patients with mitral stenosis Tricuspid stenosis is an operable lesion Organic and relative tricuspid insufficiency are likely to improve after mitral valvuloplasty

Patients with severe pulmonary vascular disease show marked improvement postoperatively those with the highest pulmonary arterial pressure benefit most The change is more rapid than could be expected from subsidence of vascular changes suggesting that the hypertension in part is functional Significant independent pulmonary disease may affect risk and prognosis and must be carefully evaluated before surgery Subacute bacterial endocarditis contraindicates surgery until the disease has been treated and cured

It seldom is necessary to add the hazard of an operation to pregnancy However some who have pure mitral stenosis who would have been in group III or IV before pregnancy definitely should have valvuloplasty The risk during the 1st trimester is little greater than in nonpregnant women Ris' is increased from the 4th to 8th months and all factors mus be carefully weighed before surgery is recommended

Many poor results and regressions after mitral surgery are due to inadequate operations rather than refusion of the valve Refusion occasionally occurs usually after 5 years

When a patient with clinically pure aortic stenosis with no contraindications shows progressive disabling cardiovascular symptoms the left heart should be catheterized When stenosis is severe operation is indicated Contraindications include coronary atherosclerosis myocardial infarction severe aortic regurgitation rheumatic activity bacterial endocarditis and intractable congestive heart failure Those with significant aortic stenosis and stationary cardiac symptoms may be considered for surgery provided severe aortic stenosis can be shown hemodynamically

Patients with asymptomatic severe aortic stenosis may eventually prove to be the best surgical group but should not be considered for operation until more is known about the long range effects of aortic valvulotomy The limitations of calcific pathology probably will make such early surgery improper until valve replacement is possible

**Management of Circulatory Inflammatory and Metabolic Complications of Mitral Valvulotomy** Mitral valvulotomy in selected uncomplicated cases carries a low mortality of about 5% However various problems may arise postoperatively and these are reviewed by A V N Goodyer and W W L Glenn[7] (Yale Univ ) from their experience with 250 cardiotomies After surgery pulse rate and body temperature are increased for 1 4 days There generally is remarkable increase in cardiac reserve estimated by the relief of exertional dyspnea although objective measurements indicate persistent hemodynamic abnormalities Circulatory complications are commonest during the 1st week manifested by prolonged hypotension or acute congestive heart failure usually associated with rapid ventricular response to acute or chronic atrial flutter fibrillation These occur more often in seriously disabled patients particularly if preoperative preparation was inadequate or blood and fluid losses or cardiac trauma were excessive

The blood pressure may begin to fall during anesthesia induction and may continue for several days with cerebral symptoms diaphoresis coldness of the skin and acrocyanosis Yet hypotension may be reversible Intravascular or total fluid losses if depleted should be replenished Excessive replacement may cause congestive heart failure and pulmonary edema The blood pressure may improve if the head and thorax are moderately elevated until the neck veins collapse When hypotension persists intravenous infusions of norepinephrine should be maintained as long as 12-48 hours if necessary in amounts that maintain systolic pressure between 80 and 100 Overdosage must be avoided because it may cause arrhythmias or pulmonary engorgement and edema If response to norepinephrine is inadequate 100 mg hydrocortisone intravenously every 3 hours for 3 doses may restore vascular responsiveness

Acute cardiac failure associated with atrial flutter and fi

(7) N w E gl d J M d 257 735 43 Oct. 17 1957

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intake postoperatively to 1 500 2 000 cc daily Mild hyponatremia that occurs despite this low water load tends to be relieved spontaneously by water diuresis in a few days and requires no treatment In severe hyponatremia remediable primary circulatory abnormalities should be sought and corrected One or more infusions of salt poor human albumin may help A trial of hypertonic saline solution may be indicated when actual salt depletion has occurred or is suspected

**Surgical Treatment of Mitral Insufficiency by Total Circumferential Purse String Suture of Mitral Ring** Incidence of mitral insufficiency appears high Most of the deaths from rheumatic heart disease occur in patients with valvular lesions these lesions eventually lead to failure and death There are at least two general indications for correction of mitral insufficiency patients with mitral stenosis in whom the concomitant insufficiency contraindicates further opening of the valve and those with pure or predominant mitral insufficiency The more severe the myocardial impairment the greater is the urgency for relieving the valvular defect

Robert P Glover and Julio C Davila[8] (Presbyterian Hosp Philadelphia) suggest a new approach to this problem based on the principle of reducing the size of the orifice the valve must occlude The procedure is accomplished best by controlled constriction of the left atrioventricular ring This approach avoids intracardiac foreign bodies and uses fully the available valvular elements It does not damage existing valvular structures nor reduce the capacity of the orifice On anatomic and physiologic grounds after extensive laboratory experience with many modifications the best method appears to be total circumferential constriction of mitral purse string The technic consists of placing an encircling suture around the mitral valve ring Thi accurately reduces the ring to the optimum degree and provides permanent stability preventing future dilatation even when the regurgitation is not totally eliminated

The procedure was completed in 12 patients each in the terminal phase of valvular disease in dire distress and apparently in irreversible cardiopulmonary hepatic disease Four are living and improved and of these 4 2 are living 1 year after surgery the longest reported survival after any surgery for mitral regurgitation Two did not survive surgery

(8) C 1 t on 15 661 681 M y 1957

brillation may interrupt prior sinus rhythm arrhythmia has occurred occasionally despite preoperative digitalization Quinidine not only does not prevent such arrhythmia but has caused additional serious difficulties such as conduction abnormalities and cardiac arrest The safest treatment is to try to slow ventricular response by one or more increments of lanatoside C If fibrillation persists during convalescence conversion should be attempted with quinidine

When cardiac failure persists after apparently adequate mitral valvulotomy the cause probably is persistent severe pulmonary vascular disease one or more major valvular or myocardial abnormalities in addition to mitral stenosis chronic atrial fibrillation recurrent rheumatic activity and recurring pulmonary emboli Bacterial endocarditis may smolder for many weeks without overt signs The usual inflammatory changes after mitral valvulotomy are chest pain fever pleural effusion pericarditis and elevated C reactive protein for 3 10 days Undue prolongation of such symptoms or their later flare up constitute the syndrome of pleuropericarditis after cardiotomy Characteristically they arise within a month of operation the chest pain usually is pleuritic commonly referred to the left shoulder and often described as an aching stiffness of the entire left side of the chest or precordium Pleural and pericardial effusions usually are minimal but occasionally are large The sequence may be repeated several times Its cause is unknown The manifestations are characteristic of acute rheumatic fever benign nonspecific pleuropericarditis and the postmyocardial infarction syndrome These patients tend to have normal sinus rhythm severe mitral stenosis and a recently elevated antistreptolysin O titer before surgery The syndrome tends to follow a remittent course though often recurring in attacks of declining severity Prognosis is not affected Symptomatic treatment often may be all that is required The more severe cases respond to steroids

Hyponatremia is a common metabolic complication of mitral valvulotomy The positive balance of water after surgery explains the hyponatremia in most patients Loss of sodium chloride from the extracellular compartment rarely could be implicated The electrolyte abnormality was due to dilution because of unusual retention of ordinary water intake It can be reduced in degree and frequency by restricting water

flow by significantly increasing the thickness of their walls The principal changes are medial hypertrophy intimal thickness due to fibroelastic proliferation hyaline deposits and thickened endothelium and thickening splitting and hyperplasia of the elastic lamina These changes produce varying degrees of narrowing of the vascular lumens It has been inferred that they result from increased pulmonary flow and pressure load The magnitude of rise in systolic and diastolic pressure in the pulmonary artery after exercise and the time taken by it to return to normal may roughly quantitate the loss of pulmonary reserve

The ideal time to repair a ventricular septal defect is when pulmonary artery pressures are below 75% of systemic arterial pressure At this time the patients have a large left to right shunt as suggested by a diastolic overload pattern of the left ventricle in the ECG Significant drop of pulmonary artery pressure after injection of aminophylline into the catheter favors good postoperative result The superimposi*tion of a systolic overloading pattern of the right ventricle* associated with flattening of T waves in the left sided leads mitigates the chances for good result

All interatrial septal defects should be repaired except in patients who have reversed shunts and cyanosis or those without symptoms in whom shunt flow is insignificant without roentgenographic or ECG abnormalities

In pulmonic valve stenosis when the systolic gradient is 20 mm Hg or more surgery is indicated even if the patient is asymptomatic especially when ECG signs are present If possible the operation should be deferred in children to age 4 6

In 9 patients direct visual repair was carried out The severity and site of the pulmonic stenosis determined the outcome *Infundibular pulmonic stenosis was more difficult* technically and the risk was greater The size of the ventricular septal defect or presence or absence of overriding of the aorta did not affect the ultimate outcome Results were best in low grade pulmonic stenosis When it was extreme *and pressure in the pulmonary artery was 10 20* mm Hg the patient usually died postoperatively For good result the pulmonary bed must be adequately developed to take the increased blood flow after opening of the pulmonic valve

1 died in the late postoperative period and the other 5 survived surgery up to 5 months with initial improvement Improvement was transient in 3 and lasting in 2 but these 2 patients died suddenly of unknown cause

In view of the excellent mechanical correction of regurgitation in 11 of 12 patients and the good clinical results in 4 survivors this corrective procedure should be attempted in patients who are somewhat better candidates

Since submission of this article for publication an additional 24 patients all in far advanced terminal stage IV had this procedure making a total of 36 Of these 42% are improved representing pure clinical salvage In 5 patients operated on most recently who had less advanced disease improvement was dramatic and no mortality occurred

**Indications and Contraindications for Open Cardiac Surgery** Henry A Zimmerman Earle B Kay John MacKrell and M P Sambhi[9] (St Vincent s Charity Hosp Cleveland) review their experiences with 72 patients who had open cardiotomy In isolated interventricular septal defects patients in whom oxygen content rose no more than 1 vol % from the right atrium to the right ventricle were considered to have benign Roger s disease The small size of the septal defect prevents any sizable shunt to cause any significant increase in pulmonary blood flow These patients should be reevaluated after 2 3 years to make sure the condition is not progressing

Of patients with interventricular septal defects in whom pressure of the pulmonary arteries was 80 mm Hg or higher none achieved a good result from surgery All who failed to survive had pressures at this level with almost equal pressures in the pulmonary and systemic arteries However all who had pressures well below 80 mm Hg in the pulmonary arteries did well postoperatively and pulmonary artery pressure did not exceed 75 80% of the systemic arterial pressure Those who died usually did so in the immediate postoperative period with low systemic arterial pressures and pulmonary edema suggesting that left not right ventricular failure is responsible

In interventricular septal defects the small muscular pulmonary arteries may respond to increased pulmonary blood

(9) Am H t J 54 727 741 N mber 1957

heart failure is suspected postoperatively digitalis is started

Complete heart block which occurs transiently as the patient s heart takes over in the operating room is fairly frequent and not particularly worrisome but if from the time of operation heart block persists with an idioventricular rate under 50/minute it is an ill omen for survival

The external electric pacemaker was lifesaving in at least 2 patients maintaining an adequate heart beat for 4 and 8 days Isoproterenol (Isuprel®) rectally sublingually or intravenously was valuable in maintaining the ventricular pacemaker Molar sodium lactate used on a number of occasions had no effect on the block Pulmonary complications were common in the first 50 patients but are now relatively uncommon because of careful attention to ventilation of the lungs at operation avoidance of hypervolemia and precise surgical procedures Apparent sudden deaths have been eliminated through gradual perfection and refinement of technics use of excellent perfusion flow and avoidance of tissue anoxia and metabolic acidosis Incomplete repairs especially in tetralogy accounted for some deaths hypervolemia for others and heart block for about 8% In 4 patients bacterial endocarditis developed with pseudomonas resistant to the usual antibiotics as the infecting bacterium Two of the 4 died and 1 was moribund The sterilizing technics for the pump oxygenator have since been altered Mortality rate for surgery in young infants was distressingly high (about 15%) but their condition was critical Mortality rate *in 38 patients with tetralogy of Fallot was 26%*

The cardiac defects cured by direct vision intracardiac operations with use of the extracorporeal pump oxygenator include (1) ventricular septal defect (2) atrial septal defect (3) common atrioventricular canal with adequate mitral valve (4) anomalous pulmonary venous connection with atypical atrial septal defect (5) complete anomalous pulmonary venous connection (6) pulmonary stenosis—infundibular or valvular with intact ventricular septum or both (7) tetralogy of Fallot cyanotic or noncyanotic (8) aortic sinus aneurysm with rupture with and without ventricular septal defect (9) congenital aortic stenosis and (10) combined subaortic and subpulmonary valvular stenosis Potassium asystole has worked out exceptionally well

**Clinical Problems Related to Surgical Repair of Intracardiac Defects with Aid of Extracorporeal Pump Oxygenator** are reviewed by Howard B Burchell[1] (Mayo Clinic) In many instances clinical data are sufficient to recommend surgery without cardiac catheterization or angiocardiography If it can be determined with reasonable certainty that the patient has 2 ventricles and 2 great vessels has no gross valvular defect and has or has not arterial desaturation dependent on presence or absence of pulmonary stenosis he is potentially a surgical candidate

Cardiac catheterization is often performed when the clinical problems are atypical The main criterion for surgery in ventricular septal defects in absence of pulmonary stenosis is a left to right shunt If the shunt is right to left pulmonary vascular changes must be assumed If the left to right leak is small because the orifice is small surgery is not mandatory if it is small because of right ventricular hypertension and pulmonary vascular changes surgical repair is fraught with danger and late results are unpredictable

The ECG is of inestimable value Patients with the atrioventricularis commune defect (so called ostium primum defect) often have a characteristic ECG i e left axis deviation in the standard leads and apparent partial right bundle branch block in the precordial leads After surgical repair of a ventricular septal defect right bundle branch block of classic conformation is often noted

Before and after surgery infants and children are weighed After surgery they are under constant surveillance in a recovery ward with special attention given to drainage from thoracic cavities urinary flow and other fluid loss Fluids are replaced as necessary based on an accumulative chart with entries every 15 minutes for the 1st hour or so The water requirements are about 500 ml /sq m the 1st day and 750 the 2d and 3d days The data indicated a state of antidiuresis during the first 36 hours

Excessive bleeding is rare Severe hypotension occurs in some patients and norepinephrine (Levophed®) is sometimes lifesaving Any patient who has or has had heart failure or has atrial fibrillation receives full doses of digitalis preoperatively with maintenance doses after surgery If

(1) C c lat on 16 976 987 Dec mbe 1957

Of the 98 operations 88 were total cardiopulmonary by pass and 10 were unilateral bypass Total mortality was 29 5% but many patients were in advanced chronic cardiac failure at operation which was a last resort In several pa tients surgically uncorrectible anomalies such as endocar dial fibroelastosis and extremely complicated septal defects of the atrioventricularis communis type were encountered Of 12 patients with large atrial septal defects only 2 (16 6%) died One was a woman who had been in intracta ble congestive failure for years the other death was due to a massive coronary air embolism Open cardiotomy was used for repair of the tetralogy of Fallot in 7 patients none of whom was severely cyanotic and 3 died presumably of con gestive failure during the first 24 hours

**Coronary Arteriovenous Fistula.** Because coronary arte riovenous fistulas are potentially serious lesions that have been treated successfully by surgery Israel Steinberg Janet S Baldwin and Charles T Dotter[3] consider their diagnosis a matter of concern to all physicians A review of the lit erature revealed reports of 13 cases in which the fistulas were found at autopsy and 8 in which diagnosis was established during life by thoracotomy or cardiac catheterization The authors add an additional case diagnosed during life

Girl 6 asymptomatic and energetic was seen because of a heart murmur It was loudest in the left 4th and 5th interspaces at the midclavicular line less intense at the left sternal border and faintly audible at the angle of the left scapula A peculiar superficial quality was noted by all observers The murmur moderately high pitched and hollow began late in systole was of greatest intensity during early diastole but was present during all of diastole Angiocardiog raphy revealed a tortuous markedly dilated vessel in the anterolateral wall of the heart which filled simultaneously with the ascending aorta. During 7 years of follow up there has been no change

Ages of the 22 patients ranged from 13 months to 85 years Cardiovascular symptoms occurred in 11 patients but in only 6 was the lesion regarded as responsible Cardiac symptoms are those of heart failure due to the increased cardiac output secondary to the left to right shunt Five pa tients had clear cut evidence of chronic heart failure Elec trocardiograms were unremarkable Cardiac catheterization performed on 5 patients showed shunted blood to enter the left atrium in 1 and therefore shunt volume could not be calculated In the other 4 the shunt volumes ranged from

(3) C 1 t on 17 37 390 M h 1958

Temporary Extracorporeal Circulation in Surgical Treatment of Cardiac and Aortic Disease Report of 98 Cases is presented by Denton A Cooley Benjamin A Belmonte, Michael E De Bakey and Joseph R Latson (Baylor Univ) Temporary controlled extracorporeal circulation of two types has been used total cardiopulmonary bypass and simple unilateral bypass shunting blood from venous to venous or arterial to arterial regions The pump oxygenator was of the bubble type The blood was defoamed in a polyethylene bottle containing an antifoam agent Dow Corning Antifoam A Potassium induced cardiac arrest was used as an adjunct to produce a completely quiet and bloodless field

For large defects in the septum polyvinyl sponge (Ivalon) patches were used to tamponade the closure using 00 and 000 black silk sutures Small defects were closed with multiple interrupted silk sutures using one row of mattress sutures and a second row of simple interrupted sutures With the use of potassium induced cardiac arrest almost all defects large or small could be closed with only multiple interrupted silk sutures

Defects in the membranous septum were found in 34 of 45 patients in the posterior superior position of the muscular portion in 4 low in the muscular septum in 4 and above the crista supraventricularis in 3 More than one defect was present in 5

When only venovenous or arterioarterial shunting was necessary only part of the cardiovascular system was used without an oxygenator For example in 1 patient who had combined infundibular and valvular pulmonic stenosis with intact ventricular septum and right ventricular hypertrophy cardiac inflow occlusion was produced and cava blood pumped into the pulmonary artery at a rate of 1 500 cc/minute Right ventriculotomy was used for complete infundibular resection and pulmonary valvulotomy under direct vision For resection and grafting of the aorta, unilateral bypass was used in bypassing the descending thoracic aorta to prevent spinal cord ischemia distal to the occluding clamps Oxygenated blood from the left auricular appendage was passed through a plastic cannula and pumped into the abdominal aorta through a catheter threaded up a femoral artery

( ) Ann Su g 145 898-914 J ne 19 7

phylactically in circumstances likely to induce anginal pain or promptly if pain occurs is valuable Visammin (khellin) dioxyline (Paveril®) the xanthine drugs and papaverine have proved ineffective Alcohol is neither indicated nor contraindicated The long acting nitrites such as Metamine® Nitroglyn® Choledyl® and Peritrate® often are prescribed but their effectiveness is doubtful Intravenous heparin has been of no more benefit than placebo injections

Radioactive iodine induced hypothyroidism is used with increasing frequency in angina and has been reported effective in 75% of cases This is an important advance if the patients studied had unquestionably severe and intractable angina and if the criteria of improvement were accurate No satisfactory explanation has been offered as to the mechanism involved Induction of a new disease myxedema in an attempt to relieve another is an undesirable feature of the treatment Other medical measures should be given a thorough *trial before radioactive iodine is used*

Bilateral rhizotomy and sympathetic ganglionectomy for relief of anginal pain have been abandoned Introduction of a graft between the aorta and coronary sinus with partial constriction of the coronary sinus at a subsequent operation carries too high a mortality Cardiopericardiopexy is intended to revascularize the myocardium by producing a chronic pericardial inflammatory reaction and in turn stimulating intercoronary and extracardiac anastomoses Even in experienced hands these pericardial operations have early mortality of 5 10% Significant reduction in pain is reported in 75 80% of cases but results are difficult to evaluate The tiny vascular channels are probably insignificant as collateral circulation

Myocardial revascularization of ischemic myocardium by implanting an internal mammary artery directly into the wall of the left ventricle reportedly improves angina pectoris and work tolerance in 60% of patients Mortality is under 5% in those without angina pectoris at rest and 50% in those with status anginosus The grafted artery does not remain patent after a few months and there is no acceptable evidence of increased circulation The claim that internal mammary artery ligation produces a significant collateral circulation is even more difficult to accept than such a claim for the other operative procedures

26 to 55% of the left ventricular output The findings can mimic those of interatrial and interventricular septal defects patent ductus arteriosus or aorticopulmonary septal defects unless the blood oxygen content is determined from various regions particularly from the coronary vein if this is the site of the communication

Conventional x rays may reveal cardiac enlargement and some prominence of pulmonary arteries Special contrast visualization specifically aids in establishing the diagnosis by revealing moderate to large sized coronary artery aneurysms Coronary arteriography by the controlled approach of occlusion aortography offers the most precise means for anatomic diagnosis of coronary arteriovenous fistula available during life probably superior to surgical exploration

In all 4 cases in which the involved coronary artery or branch was ligated cure appears to have been effected since the continuous murmur disappeared in all cases and symptoms disappeared in the 2 in which they were present

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## CORONARY DISEASE

**Recent Advances in Coronary Heart Disease and Its Management** are reviewed by Charles K Friedberg[4] (Mount Sinai Hosp New York) Diagnosis of angina pectoris depends on a history of the exact character location and radiation of pain the circumstances under which it occurs and the effect of resting and of nitroglycerin The 2 step exercise ECG test has gained widespread usage but in clinical practice need for the test is questionable for patients who are co operative and reasonably intelligent Final diagnosis should never depend on the test but on the history and clinical observation Often the test is negative in unequivocal angina pectoris Attempts to standardize it with a different number of trips prescribed according to age sex and weight probably are of little value compared with differences in physical capacity and training The test should not be performed when the patient appears ill has chest pain at the time or has an abnormal ECG at rest

In treating angina pectoris sublingual nitroglycerin pro

(4) N w Y k J M d 57 3643 3659 N v 15 1957

notes a serious not a mild disease The new oral anticoagulants show no striking advantage over Dicumarol®

Use of continuous controlled intravenous infusions of *norepinephrine (Levophed®) now is generally* accepted as the treatment for shock in myocardial infarction The effect is difficult to evaluate because of the varied criteria used The drug effectively raises blood pressure and perhaps sometimes overcomes shock It is uncertain whether Levophed® significantly reduces the mortality rate from shock in myocardial infarction

Evidence that high fat diets cause coronary heart disease is not sufficient to justify a revolutionary change in diet Physicians generally are advocating a sharp reduction in fat intake Efforts also have been made to control lipid metabolism by prescribing lipotropic agents or sitosterols or by adding corn oil to the diet If high fat intake is responsible *for coronary heart disease then reduction in fat intake* appears to be more practical and probably more effective Use of estrogens has not found general acceptance

**Atrial Coronary Arteries in Man** Thomas N James and George E Burch[5] (Tulane Univ ) studied the atrial coronary arteries of 43 human hearts by *injecting them then digesting* away the tissues The largest atrial artery was that supplying the region of the sinoatrial node It arose from the left coronary artery in *39%* of hearts and from the right coronary artery in 61% Its general course from either artery was to the anterior interatrial septum and thence to an encircling termination at the base of the superior vena cava

A specific artery supplied the region of the atrioventricular *node It arose from the right coronary artery at the pos*terior junction of the interatrial and interventricular septa in 83% of hearts The right coronary artery at this location made a U turn beneath the posterior descending vein

Many other atrial coronary arteries were noted but were small and variable One of their principal functions may be that of potential sources of collateral circulation

Whether or not sinoatrial node block develops depends on (1) the *coronary artery from which the ramus ostii cavae* superioris originates (2) whether or not an occlusion is distal or proximal to the origin (3) the effectiveness of the collateral circulation to the sinoatrial node including the

(5) C 1 t 17 90 98 J ry 1958

Clinical manifestations of coronary heart disease probably are related to atherosclerosis per se only when atherosclerosis is extreme and narrows a major coronary artery In most cases thrombosis is responsible Although atherosclerosis is the major underlying predisposing factor other undetermined factors probably are responsible for the actual thrombosis Recent studies suggest that the blood becomes hypercoagulable for several hours after a fatty meal but not after carbohydrate meals None of the studies is definitive and conflicting evidence has been presented Studies in various laboratories have failed to substantiate the claim that individual susceptibility to coronary heart disease may be predicted from the concentration of lipoproteins as measured in the ultracentrifuge as $S_f$ units

Leukocytosis an increase in erythrocyte sedimentation rate and presence of C reactive protein are nonspecific indexes of myocardial infarction Marked elevation of serum glutamic oxalacetic transaminase begins about 6 hours after acute myocardial infarction reaches a peak after 24-48 hours and usually returns to normal within 3 5 days Similar changes have been described for serum lactic dehydrogenase Continued studies are needed to determine the exact diagnostic and differential diagnostic value of these enzyme determinations

The outlook after recovery from acute myocardial infarction is more favorable than hitherto believed More than 75% of those recovering from a first attack are able to return to work Bed rest remains the mainstay of therapy Bedside commode self feeding earlier use of a chair bathroom privileges and earlier ambulation are used more liberally now than formerly One should not become too preoccupied with the advantages or disadvantages of the armchair treatment because it probably is of little or no importance in the ultimate outlook in patients who do not have severe left sided congestive heart failure Reported observations indicate however that patients with acute myocardial infarction can recover whether they sit in a chair or lie in bed

Anticoagulation reduces the mortality and incidence of thromboembolism There is a strong trend to omit anticoagulants in so called mild cases but at onset of the attack it is difficult to determine which will be mild Even in so called mild cases as a group the mortality is 3 5% ... de

be made to disappear within a few minutes after intravenous injection of heparin This effect which does not occur in vitro is independent of the anticoagulant effect of heparin Plasma obtained after intravenous injection of heparin contains a lipase, different from all other known lipases which splits only neutral fats bound to protein This consists of heparin or a heparin like substance as coenzyme and a specific protein as apoenzyme The clearing factor is found in plasma and within cells especially in adipose tissue and myocardium but only rarely in brain tissue

The clearing mechanism is of principal clinical interest in atherosclerosis In many cases of proved atherosclerosis (mostly in patients with coronary infarcts) there is an increase of beta lipoprotein and lipoprotein of $S_f$ type 10 20 These types have etiologic significance in atheromatosis of coronary vessels Heparin tends to normalize the changed spectra in the ultracentrifuge and lipid electrophoretic patterns From protamine titrations of serum it is also known that a heparin like substance normally present in serum is lacking or present only in small amounts in serum of atherosclerotic patients otherwise an unchanged proportion between blood heparin and concentration of lipoprotein of lower density should exist In patients with atherosclerosis spontaneous clearing of an alimentary lipemia and also heparin induced clearing takes significantly longer and reaches a definitely smaller maximum than in normal persons

Clearing activity in plasma of atherosclerotics shows a pathologic value in a definitely higher percentage than in determinations of serum lipid alone If heparin is given in the fasting state in normal persons there is usually no change in lipid electrophoresis whereas in atherosclerotics even in those with normal serum lipid values there is slight acceleration of motility of lipoprotein similar to that in mild hyperlipemia Recent in vitro studies indicate the possibility of pathologically increased clearance factor antagonists in atherosclerosis Mast cells as carriers of endogenous heparin are piled up at the borders of atherosclerotic plaques in the aorta in man Possibly by the effect of heparin neutral fat can be isolated from atherosclerotic plaques while cholesterol is retained This would explain the high cholesterol content of atherosclerotic foci In rabbits the animals most

besian channels and (4) the circulatory demands of the sinoatrial node area at the time Since the artery to the sino atrial node arises more frequently from the right coronary artery shifting pacemaker atrial fibrillation sinoatrial node block and other manifestations of sinoatrial node ischemia should be more frequent with right coronary disease

Disturbances in function of the atrioventricular node and bundle of His should occur less frequently with occlusion of the left coronary artery since it supplied the atrioven tricular node in only 10% of the hearts studied

**Effect of β Sitosterol on Cholesterol Induced Atheroma in Rabbits with High Blood Pressure** was investigated by R H Heptinstall and K A Porter[6] (London) Experiments in chicks rabbits and rats have shown that the large rise in blood cholesterol levels which usually follows the feeding of cholesterol can be prevented by adding plant sterols to the diet The most widely distributed plant sterols are the sitosterols—β sitosterol in cottonseed oil tall oil and wheat germ oil and γ sitosterol the principal sterol in soybean oil and a minor component of wheat germ and rye germ oil

Rabbits with high blood pressure show considerably more atheroma in the aorta than do rabbits with normal pressure and such animals provide a more rigorous test of the effi cacy of plant sterols in preventing cholesterol induced ath eroma High blood pressure was induced by removing one kidney and 2 weeks later applying a silver clip to the left renal artery Cholesterol was then fed to one group of rab bits and combined cholesterol and β sitosterol to another

Serum total cholesterol levels were significantly lower at all stages of the experiment in the group receiving β sitos terol and the amount of aortic atheroma was considerably less The latter was probably due to the smaller amount of circulating cholesterol available for deposit The results in dicated that even in the presence of high blood pressure sitosterol can clearly reduce the amount of atheroma pro duced by cholesterol feeding

**Heparin Clearing Factor and Lipid Metabolism** are dis cussed by H Scholl and G Schettler[7] (Stuttgart) Animal experiments have shown that serum turbidity caused by intake of a fatty meal which persists for several hours can

(6) B t. J E pe P th 38 49 54 F b u ry 1957
(7) De tsch m d W hn hr 82 1405 1410 Aug 30 1957

structed to ingest 1 1½ oz corn oil (Mazola) before each meal Five were given no dietary restriction and 18 were instructed to avoid butterfat margarine hydrogenated vegetable oils and more than 1 egg daily but were allowed meat twice daily

Of the 23 patients 16 (70%) had at least a 15% drop in serum cholesterol from an average of 271 mg/100 ml to 208 and a drop in serum phospholipid from 287/100 ml to 231 Small decreases in serum cholesterol from 9% to 14% occurred in 6 others One patient showed no significant change A sizable decrease in serum cholesterol often was apparent after only a week of corn oil ingestion but in a few patients the decrease was gradual and delayed over a month Five patients reported considerable relief from anginal attacks while ingesting corn oil but this is difficult to evaluate because it is well known that placebo therapy can greatly relieve anginal symptoms

These results are highly significant statistically If corn oil had no real effect on serum cholesterol and phospholipid levels random increases in serum concentration would have been as frequent as the decreases Actually all had decreases in the concentration of cholesterol and phospholipid during ingestion of corn oil Since there was little or no weight gain intake of other foods must have been curtailed, including intake of saturated fats This undoubtedly contributed to the decrease in serum cholesterol The drop in cholesterol was maintained continuously during 1 year of corn oil ingestion

► [This study and the 2 subsequent articles indicate some of the uncertainty which still prevails in regard to the exact role of fat and other dietary factors in the production of atherosclerosis in general and particularly of the coronary arteries However this uncertainty should not raise serious doubt concerning the well supported evidence that diet and particularly fat is of importance Pending more comprehensive information it seems highly desirable in patients with coronary disease to continue to restrict fats and more particularly the hydrogenated fats which are mainly those of animal origin Certainly obese subjects should have the additional restriction on total calories The idea that a large intake of unsaturated fats is positively beneficial is intriguing but merits further experimental study before being widely accepted —Ed ]

**Fats Cholesterol and Coronary Heart Disease** Recent advances are reviewed by Norman Jolliffe[9] (Dept of Health New York City) Atherosclerosis is the key to coronary heart disease If atherosclerosis can be prevented delayed

(9) N w Y k J M d 57 2684 2691 A g 15 1957

susceptible to cholesterol atherosclerosis the smallest number of mast cells are histologically recognizable

In individual cases of idiopathic hyperlipemia lack of clearance with heparin was observed and related to deficiency in clearing factor Possibly these cases represent the clinical manifestation of a primary insufficiency of clearing factor

Success of heparin therapy for atherosclerosis can be evaluated objectively Prolonged heparin therapy (200 mg subcutaneously twice a week for 2 years) in 105 patients with coronary infarct for over 3 months was accompanied by 4 cardiovascular deaths whereas 21 of 117 patients treated without heparin during the same period died of cardiovascular causes The corresponding ratio of nonlethal reinfarctions was 3 13 The effect of heparin on blood coagulation was slight with this method of administration

In most of 36 patients with atherosclerotic diseases an increase of arteriovenous $O_2$ difference of about 25 30% was demonstrated With obliterating atherosclerosis of the lower extremities pletysmographically verified improvement was noted Accessible vessels of eyegrounds showed total or subtotal regression of vascular closure under heparin treatment Results of therapy of angina pectoris without demonstrable coronary infarct are contradictory with reports of failures and of definite improvement Causes of angina pectoris are so numerous that satisfactory results cannot always be expected In proved anomalies of fat metabolism heparin therapy appears worth a trial in anginal conditions In treatment of a fresh heart infarct the anticoagulant effect of heparin is combined with that on fat metabolism

**Efficacy of Corn Oil in Lowering Serum Cholesterol of Patients with Coronary Atherosclerosis** According to recent reports ingestion of highly unsaturated fats under controlled conditions has lowered serum cholesterol To determine whether this could be accomplished in clinical practice where diets are not rigidly controlled and meat often is eaten twice daily Louis Tobian and Naip Tuna[8] (Univ of Minnesota) selected for study 23 patients with clinical coronary atherosclerosis (15 with a history of myocardial infarction and 18 with angina pectoris) After the initial serum cholesterol level was determined each patient was in

(8) Am J M Sc 235 133 137 F bru ry 1958

els of total cholesterol in the serum or the beta lipoprotein fraction These parallels are supported by the higher prevalence of coronary heart disease in diabetes myxedema nephrosis and lipid dystrophies in which hypercholesteremia is a common factor

Without a high intake of saturated and hydrogenated fats stress and strain physical indolence obesity luxury living or tobacco are only minor factors in producing the high incidence of coronary heart disease below age 65 If a favorable change in the cholesterol lipoprotein system can be produced and maintained by diet and favorably change the morbidity and mortality of coronary heart disease the eating habits of the American male must be modified new methods developed to process and plasticize fats or a way found to fortify the naturally or artificially saturated fats with factors present in certain marine and vegetable oils

Diet and Coronary Thombosis Hypothesis and Fact are reviewed by John Yudkin[1] (Univ of London) from all the data available Various hypotheses have been propounded but not all the epidemiologic data fit these simple explanations One hypothesis relates coronary mortality to total fat consumption by country The correlation is excellent when the figures are obtained from Japan Italy West Germany Switzerland and New Zealand However in Norway Denmark the United Kingdom Canada and the United States the range of coronary mortality is nearly fourfold but the daily intake of fat is not significantly changed

Some have quoted fat intake not as the total amount but as the percentage of total calories derived from fat There is no physiologic reason for this and when the foregoing calculations are repeated the same results are obtained Some have maintained that the culprit is butterfat or animal fats but the figures do not support this and there is no relationship positive or negative between the intake of vegetable fat and coronary mortality Hydrogenated fats—margarine compound fats and shortenings—are also without correlation The most obvious discrepancy is in Norway which has by far the highest consumption of these fats The intake of other nutrients total protein animal protein sugar and total caloric intake are also without exact relationship but the relationships which do exist suggest that coronary thrombosis

(1) Lancet 2 155 162 J ly 27 1957

or postponed the mortality rate in the age group 45-64 will be markedly decreased and the average life span greatly lengthened In the last 30 years the incidence of atherosclerosis has increased—more than can be accounted for by fashion in diagnosis an older population and improved diagnostic methods Young people are affected more often than formerly

Environment is a significant cause of coronary heart disease though heredity and genetic factors may determine the degree of susceptibility Deficiencies in diet other than pyridoxine and certain amino acids are not causally related and these operate by disturbing fat metabolism Obesity is an important lesser factor but in itself cannot explain the differences found in population groups Stress and strain may also be lesser factors Differences in physical activity do not explain the large differences in serum cholesterol and by inference the rate of coronary heart disease when groups with different dietary habits degrees of physical activity and rates of coronary heart disease are observed for purposes of comparison

The environmental factor that correlates best with coronary heart disease is total fat consumption expressed as per cent of total calories Populations with fat intakes approximately 40% of total calories have high death rates below 20% low death rates with intermediate intakes intermediate death rates Within the United States the increasing incidence of coronary artery disease correlates with the total fat consumption as obtained from figures of the Department of Agriculture

Diets containing highly saturated fats result in high levels of blood cholesterol Substitution or addition of certain oils rich in unsaturated fatty acids consistently decreases the serum concentration of beta lipoprotein total cholesterol When these substituted oils are hydrogenated and then fed they no longer decrease the serum cholesterol but raise it as do certain fats which are naturally highly saturated such as butter This does not prove that saturation or unsaturation is the fundamental cause for changes in the cholesterol system but it appears to be an important factor

A triangular relation exists between (1) amount and quality of fat consumed, (2) death rates from coronary heart disease particularly in men aged 45 64 and (3) blood lev

During the study period on an average the exercised animals lost 0 3 kg and the caged animals gained 0 2 kg Retrograde flow through the cannula measured collateral function and flow through the ligatures measured the degree of circumflex constriction In general the extent of collateral blood flow was proportional to the degree of constriction Exercise increased collateral communications significantly over that due to narrowing alone At the end of the experiment the circumflex artery could be completely occluded without inducing ECG changes in those animals in which good collateral supply developed In rested animals with slight circumflex narrowing significan collaterals did not develop retrograde flow was low and ECG changes after occlusion resembled those after occlusion in normal dogs In the exercised dogs that had only slight narrowing the flow rates were definitely increased Exercise clearly augmented collateral flow above that induced by constriction of the artery alone

These results agree with the studies on human hearts Identical mechanisms probably operate to develop collateral vessels in man and dogs In rested dogs that had only mild arterial narrowing the myocardium was susceptible to infarction when the vessel was suddenly occluded because collateral vessels were absent In patients with minimal vascular narrowing complete vascular occlusion is more likely to develop than in normal persons During this early stage when collateral channels have not yet developed exercise may be particularly effective in promoting collateral growth that otherwise would not occur

Since onset of coronary artery disease is not clinically recognizable it probably would be advisable to encourage middle aged asymptomatic persons to exercise Patients without recent infarcts who have angina probably also should be placed on a positive program of mild exercise that just falls short of producing pain Judicious use of early continued physical exercise may reduce the clinical manifestations of coronary artery disease

**Effect of Exercise on Blood Coagulation Time and Atherosclerosis of Cholesterol Fed Cockerels** Many investigators have suggested that lack of exercise is important in atherogenesis Nelta Hyder Warnock Thomas B Clarkson and

is associated with higher living standards, and this is supported by the parallel which exists between coronary mortality and national income per capita

In the United Kingdom the chance of a semiskilled worker dying of coronary artery disease is only about half that of a professional man The consumption of fat and of butterfat show similar trends with increasing income, but the differences are small The consumption of margarine however falls with increasing income

The number of certified deaths due to coronary thrombosis has risen almost steadily since 1928 Superficial examination of the trends in consumption of total fats suggests that this is related to trends in coronary mortality However the fall in both at the beginning of the war was followed by a rise in mortality several years before the consumption of fat had reached its full prewar level This is especially true of intake of animal fats and no relationship is seen between coronary mortality and consumption of vegetable fats hardened fats or sugar By far the best correlation with trends in coronary mortality is in the number of radio and television licenses and the number of registered motor vehicles

The available evidence does not support any hypothesis which postulates a single or major dietary cause of coronary thrombosis It is suggested that relative overconsumption of food associated with reduced physical exercise may be one of several causes of the disease More detailed information is needed and smaller groups should be studied from different regions in single countries The study would be most profitable if it were prospective rather than retrospective

**Effect of Exercise and Coronary Artery Narrowing on Coronary Collateral Circulation** Exercise may favorably affect the course of coronary artery disease by delaying progression of the disease or by stimulating growth of coronary collateral vessels or both Richard W Eckstein[2] (Western Reserve Univ ) ligated the circumflex artery in 117 dogs to various degrees of narrowing After 1 week of rest for healing the dogs were separated into two groups one was exercised 4 times daily on a treadmill the other remained at rest After 6 8 weeks the dogs were reoperated on and the size of functional anastomoses was determined by maximum flow through the circumflex artery measured by cannula

(2) C ulat on Res 5 230 235 M y 1957

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The one stage prothrombin test of Quick was used in all cases and the interval between tests was gradually increased to 10 12 or 14 days All patients were informed of the risks of overdosage and were instructed to report promptly any bruising melena hematuria or other signs of bleeding The simple rule of maintaining the prothrombin time at 2 or 2½ times the normal expressed in seconds was followed Calculation of percentage of prothrombin often leads to a false sense of security and is considered superfluous

The anticoagulant regimen was stopped by 319 patients who then served as controls An additional 417 patients not given anticoagulants also served as controls

Among the patients without frank infarction (impending infarction) 6 (6 2%) of 96 on long term anticoagulant therapy died 6 (18 7%) of 32 who stopped therapy died and 4 (40%) of 10 untreated controls died Among the patients with one infarction 73 (10%) of 735 on long term therapy 38 (18 5%) of 205 who stopped therapy and 110 (37%) of 297 untreated controls died In the group with multiple infarctions there were 52 (20%) deaths among 260 treated patients 46 (56 1%) among 82 patients who stopped treatment and 42 (38 1%) among 110 untreated controls

Hemorrhage occurred in 220 (20%) patients and was more frequent in those who had used anticoagulants for years instead of just a few weeks Only 6 deaths could be attributed fairly conclusively to hemorrhage Hematuria was the commonest form of bleeding and occurred in 110 patients a few on more than one occasion More than half of these patients resumed anticoagulants for months and years without further hematuria The benefits of long term anticoagulant therapy far outstrip the risk Since vitamin $K_1$ is rapidly effective transfusions are seldom required

The available data suggest that long term anticoagulant therapy prevents recurrent myocardial infarction

► [In patients who are having repeated frequent prolonged and usually severe anginal attacks at rest anticoagulant therapy is imperative because there s strong reason to believe that it may prevent the infarction which is impending in most such patients Some cardiologists reserve long term anticoagulant therapy for patients falling within this group or for those who have already experienced two myocardial infarctions Others believe that all patients who have had a single infarction should be treated in this manner Still others prefer to utilize this form of therapy for all patients with angina pectoris It will probably be a number of years and perhaps

Richard Stevenson[3] (East Tennessee State College) fed cockerels Purina mash until they were 3 weeks old then separated the birds into two equal groups placed them in identical cages and fed them an atherogenic ration of the mash containing 1% cholesterol and 4% peanut oil for 14 weeks The 10 control birds remained caged throughout the experiment The exercise group was forced to walk briskly for 1 hour daily 5 days a week Food consumption remained equal for the two groups during the experiment

Body weight was significantly greater serum cholesterol was significantly less vascular and hepatic cholesterol concentrations were significantly smaller and blood coagulation times were significantly longer in exercised cockerels than in the caged controls The brachiocephalic arteries were most susceptible to atherosclerotic degeneration

These data support the idea that the shorter blood coagulation times found in professional men as compared with rail road switchmen are largely related to differences in the amount of exercise taken by these two groups

► [The preceding 2 studies on animals furnish experimental support to the clinical concept of the importance of exercise in preventing clinically important coronary disease Even should further investigations show that the incidence of coronary atheroma is not affected by exercise there still remains the likelihood that the rate of widening of collateral channels is favorably influenced One sees many patients with angina pectoris who have been leading extremely restricted lives in whom the exercise tolerance rapidly begins to increase on a regimen of graded increasing exercise. Obviously the amount of effort selected should be less than that which induces the discomfort.—Ed ]

**Long Term Anticoagulant Therapy in Coronary Atherosclerosis** Results of a pooled clinical investigation of 1 091 patients who had one or more myocardial infarctions or had signs of impending infarction are presented by E Sterling Nichol John N Keyes Joseph F Borg Thomas J Coogan John J Boehrer William L Mullins Thornton Scott Robert Page George C Griffith and Edward Massie[4] Anticoagulant therapy was given to 448 patients for less than 1 year to 385 for 1 3 years and to 258 for 3 years or more Criteria for selection of patients were sufficient intelligence to comprehend the nature of the treatment and absence of blood dyscrasia or bleeding into the gastrointestinal tract or of severe renal or hepatic impairment Dicumarol® was administered to 924 patients Cumopyran® to 100 and Hedulin® Tromexan®

(3) C l t o R 5 478 480 S ptemb 1957
(4) Am Heart J 55 142 152 J n y 1958

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(7) Am H rt J 54 458 477 S ptember 1957

several decades before the exact indications become completely clarified. However the case for anticoagulant therapy is growing stronger each year not only in patients with atherosclerosis of the coronary arteries but also for those with cerebral vascular disorders —Ed.]

**Effects of Nicotinic Acid on Serum and Tissue Cholesterol in Rabbits** Oral nicotinic acid lowers serum cholesterol in human beings and in rabbits The decrease is roughly proportional to the initial elevation and rather large amounts of nicotinic acid are required These changes would be more significant if tissue cholesterol also changed To determine this point Joseph M Merrill and Janet Lemley Stone (VA Hosp Nashville Tenn ) fed rabbits stock diet stock diet with cholesterol added and stock diet with cholesterol and nicotinic acid added

In the rabbits that had nicotinic acid added to a diet high in cholesterol the expected increase in cholesterol content of serum and aorta did not occur This was not due to deposit of the cholesterol in the liver suggesting that the low serum cholesterol reflects low total tissue cholesterol

These studies confirm earlier observations that oral nicotinic acid prevents the anticipated rise in serum cholesterol and show that it effectively prevents deposit in the aorta and to a lesser extent cholesterol storage in the liver The mechanism is unknown

**Cholesteremia and Nicotinic Acid** The development of arteriosclerosis is considered to be accompanied by if not due to disturbed metabolism of lipids apparently related to the concentration of cholesterol in blood plasma Hypercholesteremia may indicate developing atherosclerosis Many attempts to reduce the cholesterol level by diet hormones vitamins and colloidal stabilizers have been reported P O O Reilly M Demay and K Kotlowski[6] (Saskatchewan Hosp Weyburn) administered 1 Gm nicotinic acid orally 3 times daily for 3 months to patients with evidence of cerebral arteriosclerosis and to subjects without

Nicotinic acid lowered the serum cholesterol in proportion to the original level Patients with the highest plasma concentrations showed the greatest percentage drop The mechanism is unknown Side reactions consisted of marked flushing and pruritus These were no greater than those seen after administration of 50-100 mg nicotinic acid and tended to diminish and usually disappear after the first few days It

(5) C c l t on Re 5 617 619 N ember 1957
(6) A M A A h Int. M d 100 797 801 No mb 1957

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(7) Am Heart J 54 458-4 7 Sept mbe 1957

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The principal observed difference between dogs with and without shock was a marked rise in the temperature pulse and respiration in the latter and little change in dogs which were in shock In humans two groups are delineated those in whom cardiac insult is so great that even marked vasoconstriction cannot maintain the blood pressure and temperature pulse and respiration remain unchanged and those in whom these values rise and shock does not occur No animal or patient showed peripheral vascular collapse—over all vasodilation and appreciable fall in temperature pulse and respiration The abnormality which indicates that a peripheral factor is present in coronary shock is failure of temperature pulse and respiration to rise in the face of a falling cardiac output and blood pressure Animal and clinical observations have indicated that heart failure is not essential in coronary shock Peripheral mechanisms not directly linked to the degree of myocardial damage apparently exist Treatment of noncoronary cardiogenic shock is directed to the specific etiology—cardiac tamponade infection tachycardia Treatment of coronary shock to date has been largely empiric

The criteria of severe coronary shock are (1) acute myocardial infarction proved by ECG or autopsy (2) systolic blood pressure of 80 mm Hg or less (except in patients with previous hypertension in whom shock may rarely occur at slightly higher levels) (3) marked oliguria or anuria pallor or cyanosis or both marked sweating cold skin and dulled sensorium and (4) absence of other causes for shock such as hemorrhage embolism infection acidosis etc For evaluation of new therapy shock should not have improved for ½ hour after pain was relieved and oxygen administered and the patient must survive at least 1 hour after initiation of new therapy Approximately 1 patient out of 5 survives if nothing is done but oxygen given and pain relieved Vasopressor drugs have reduced the mortality to 60% Any new agents to be efficacious must lower the mortalit elow 60%

The first steps are administration of morp nerol*

or Dilaudid® intravenously and prompt use of oxygen Infusions and transfusions have not lowered the mortality rate Levophed® is the most potent vasopressor It may be given via polyethylene catheter for prolonged administration The initial concentration is 8 mg /L of 5% glucose increasing to 24 mg /L if needed Should the solution infiltrate prompt injection of procaine or phentolamine (Regitine®) may prevent a slough Metaraminol (Aramine®) the newest vasopressor is about one twentieth as potent as Levophed® and can be given subcutaneously or intramuscularly as well as intravenously It also acts directly on the heart to increase myocardial contractility cardiac output and coronary blood flow besides contracting the peripheral vascular bed

Arrhythmias and congestive failure if either is present should be treated in the usual manner Steroids have been of no benefit in treating coronary shock in patients or in dogs

**Hemorrhagic Pericarditis Pleurisy and Pneumonia Complicating Recent Myocardial Infarction** Since the introduction of anticoagulant therapy for myocardial infarction hemorrhagic complications often have been attributed to this therapy W Dressler J Yurkofsy and M C Starr[8] (State Univ of New York New York City) report 3 cases of acute myocardial infarction complicated by hemorrhagic pericarditis pleurisy and pneumonia respectively in which anticoagulants were not used or were used in small amounts for only a few days

Case 1 —Man 59 had pericardial pain and congestive heart failure 6 weeks after a myocardial infarction Five weeks later symptoms and signs of pericardial effusion were noted and pericardial paracentesis revealed intensely bloody fluid He had received no anticoagulants

Case 2 —Man 54 had myocardial infarction with prolonged febrile period A loud pericardial friction rub was audible for 10 days ECG changes plus enlargement of the cardiac shadow by x ray supported a diagnosis of pericarditis with effusion Bilateral pleural effusion appeared on the 13th day Thoracentesis yielded bloody fluid There were no indications of pulmonary infarction Anticoagulants were used only for 6 days Prothrombin time never exceeded therapeutic levels and returned to normal 3 days before the hemorrhagic effusion appeared

Case 3 —Man 52 had myocardial infarction complicated by pericarditis pneumonitis and pleurisy Hemorrhagic pneumonia developed on the 3d day of illness and spread rapidly involving both lungs No micro organism was discovered Antibiotics were ineffec

(8) Am H rt J 54 42 49 J ly 1957

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dition indicated that it may be detrimental since it allows diffusion of the levarterenol also

Levarterenol is a potent and effective vasopressor When given by intravenous drip it is the most effective therapy available for combating severe hypotension and is useful in treating shock due to acute myocardial infarction cerebral arterial occlusion or pulmonary infarction or shock associated with surgical postsurgical or traumatic complications

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## ARRHYTHMIAS

**Transient Changes in Precordial T Wave of Electrocardiogram** were found by H Klepzig H Reindell and E Tecklenborg[1] (Univ of Freiburg) in 9 patients among a large series In 8 reproducibility of the pathologic ECG finding was tested after meals on the same or another day In these patients ECG was determined 9 times after meals and 5 times in the fasting state Five ECG s were taken after ingestion of potassium chloride 2 after ingestion of dextrose and 2 after ingestion of both together In 1 case an ECG was made under hypnosis Five patients were men and age range was 21 56 Seven complained of cardiac symptoms

In 8 patients whose fasting ECG was normal or nearly so pathologic deviations in the precordial T wave were seen after eating In 5 the T wave was negative in V in 4 in $V_3$ and $V_4$ in 2 in $V_5$ and in 1 in $V_6$ In 6 patients the final change took the form of Pardee s coronary T In the others there was a flat slightly negative or diphasic T in one or several leads of V to $V_6$ partly also in leads I and II In 1 patient ECG changes were not definitely correlated with food intake T wave changes disappeared under hypnosis but on the following day and numerous times thereafter the ECG was the same as before hypnosis

Several mechanisms may be responsible for these ECG changes (1) cardiac pressure from dilatation of the stomach (2) reflex disturbances due to stomach dilatation (3) changes in the blood sugar level (4) changes in potassium level (5) organic heart disease (6) special lability of the vegetative system and (7) psychic influences Mechanical

(1) De tsch m d W hnsch 82 910-913 J ne 7 1957

tive Improvement followed cortisone therapy Dicumarol® given for the first 4 days was discontinued Prothrombin time reached a maximum of 36 seconds The pulmonary process lasted for about 4 weeks.

One complication of acute myocardial infarction referred to as postmyocardial infarction syndrome is manifested by prolonged or recurrent attacks of fever and pleuropericardial pain persistent pericardial friction rub pericardial and pleural effusions and pneumonitis The manifestations are identical to those which previously had been considered due to hemorrhagic pericarditis and attributed to hemorrhage caused by anticoagulant therapy

The case in this report and similar cases previously reported as examples of hemopericardium complicating myocardial infarction present the features characteristic of the postmyocardial infarction syndrome The inflammations may be hemorrhagic The relation to anticoagulant therapy may be only coincidental It is suggested that the syndrome is due to sensitization

**Treatment of Local Ischemia Due to Levarterenol (Levophed®) Leakage with Piperoxan** Louis Pelner[9] (Swedish Hosp Brooklyn) points out that one of the drawbacks to the use of levarterenol has been the occurrence of local ischemia and skin necrosis as a result of infiltration into the skin These sequelae have also developed in the absence of infiltration Phentolamine hydrochloride (Regitine®) an antagonist of levarterenol has been used successfully to counteract the effects of local ischemia Injection into the ischemic region resulted in a return of pink color With 5 mg phentolamine in 20 cc water results were seen in 5 7 minutes

The author found that piperoxan (Benodaine®) hydrochloride also has a salutary effect in ischemia due to levarterenol infiltration A solution of piperoxan 5 mg in 2 5 cc or ¼ of an ampule was added to 17 5 cc sterile saline solution making the final dilution 5 mg in 20 cc About 0 25-0 5 cc was injected subcutaneously into the ischemic cold area first around the periphery and then within the area about 1 cm apart Within 30 50 seconds each injected area developed a pink color and became warm More than 20 cc may be used

Experience with the local use of hyaluronidase in this con

(9) J A M A 165 444 447 Oct 5 19

and if the rate is extremely high giddiness weakness vertigo visual disturbances and even syncope Attacks are often short and transient If they are of sudden onset and end suddenly and if the heart rate is 160 or more and regular atrial tachycardia or flutter is suspected If irregular atrial fibrillation occurs and the rate is over 200 accelerated A V conduction is suspected Thomas M Runge J R Oates George R. Herrmann and M R Hejtmancik[2] (Univ of Texas) set forth the diagnostic criteria to differentiate the rapid rates and bizarre ECG s of accelerated A V conduction from ventricular tachycardia flutter or fibrillation

When rapid recurring regularly spaced broad ventricular complexes are seen the first consideration is ventricular tachycardia When irregular and bizarre complexes are encountered ventricular fibrillation is suspected If the patient does not appear cadaveric is not in shock has some pink color responds to questions breathes only slightly rapidly and has a discernible pulse fibrillation cannot be the cause and flutter is unlikely Pseudoventricular fibrillation and pseudoventricular tachycardia due to the Wilson Wolff Parkinson and White syndrome or bundle of Kent syndrome with accelerated A V conduction are the probable causes

A perfectly regular rhythm at rates above 200 with P waves on every ventricular complex or on a premature contraction and with a broad bizarre QRS complex before or after a paroxysm indicates that the rhythm is supraventricular or atrial in origin An ECG between attacks shows the short P R interval slurred upstroke of R (the delta wave) and compensatory lengthening of the QRS characteristic of the false bundle branch block picture An irregular ventricular rhythm of 240 or more practically designates the presence of this syndrome since the normal auriculoventricular pathway is refractory to such rates

Procaine amide (Pronestyl®) 0 25 1 Gm given intravenously is the drug of choice It should be given slowly with constant ECG monitoring and frequent blood pressure readings If this fails quinidine should be started by mouth 0 1 Gm each hour Digitalis is rarely effective Prognosis is excellent

**Closed Chest Defibrillation of Heart** Ventricular fibrilla

(2) Am. J M Sc. 234 170 179 A gu t 1957

pressure on the heart from stretching of the stomach can not be the sole factor because the ECG changes appeared in some instances after dextrose was taken in a small quantity of water Reflex factors blood sugar and potassium levels, and organic heart disease also could not account for the ECG changes seen in these cases Lability of the vegetative nervous system appeared to be the most likely explanation Seven of the 9 patients displayed signs of disturbed circulatory regulation or of some vegetative disorder, such as hyperhidrosis dermographia or striking respiratory arrhythmia The fact that similar ECG changes can disappear with vagus blocking agents argues also for predominant influence of the vegetative nerves Anxiety and psychic conflict were significant in some cases Two patients volunteered the information that they were experiencing psychic stress In patients with unstable sympathetic systems a first ECG often shows a flatter T wave than tracings made minutes or hours later When psychic disturbances are present fluctuations from one time to another are particularly large Role of psychic factors was particularly impressive in the patient subjected to hypnosis

No general conclusion can be drawn as to the cause of inconstant pathologic changes in the precordial ECG apparently several factors may play a part Knowledge of these changes is important in avoiding diagnostic errors In the present and other reported cases false diagnoses of localized pericarditis coronary sclerosis or myocarditis were made on the basis of the ECG which contrasted with the general clinical picture Even though such ECG changes are not frequent their recognition is important

► [Although the literature now contains cores of publications emphasizing the untrustworthiness of minor T wave and S T segment changes as an index of structural cardiac disease the unfortunate habit of placing excessive emphasis on such changes is still widespread If in addition to alterations of this innocent type in the electrocardiogram the patient happens to have a chest pain due to some minor cause the likelihood of error is much greater In the absence of a characteristic clinical pattern coronary artery disease should not be diagnosed on the basis of minor T wave changes —Ed.]

**Extremely Rapid Arrhythmias and Regular Tachycardias in Paroxysms in Patients with and without Accelerated A V Conduction** The most common type of heart attack complained of by otherwise apparently normal persons consists of rapid regular or irregular heart action with palpitation

was given 70 seconds after onset of fibrillation followed by another 14 seconds later Normal sinus rhythm reappeared immediately and consciousness was regained within a few seconds She was discharged 3 days later with no apparent ill effects

*Treatment of Adams Stokes Attacks and Disturbances of* **Cardiac Conduction with Isopropylnoradrenalin (IPNA)** as aleudrin (sulfate) or Isuprel® (hydrochloride) is re ported by F Schaub M Holzmann and S Wyss[4] (Univ of Zurich) In 12 patients with the carotid sinus syndrome the effect of IPNA 1 2 tablets of Isuprel® (10 or 15 mg) or of aleudrin (20 mg) sublingually was observed after about 3 5 minutes and in fewer instances after 10 15 minutes Maxi mal effect generally was reached in 20 40 minutes Duration of effect was 40 minutes to 2 hours and averaged about 60 minutes In all patients ECG control was maintained con tinuously or at short intervals

Among these 12 patients with a ventricular or total heart arrest of several seconds IPNA led to complete disappear ance in 6 so that only an insignificant frequency interval of the otherwise unchanged sinus rhythm remained In 5 the arrest was essentially shortened by the appearance of nodes but never of ventricular substitute beats In 1 in whom be fore Isuprel® carotid sinus pressure always led to an A V rhythm with a frequency of about 28/minute frequency after Isuprel® was about 40/minute with about the same nodal rhythm In no instance did carotid sinus syndrome re main unaffected by IPNA The sinus rhythm showed a marked increase of frequency in 8 In 4 this acceleration was lacking possibly because the patients were kept in bed for 2 hours during the study In 4 duration of the originally lengthened P Q time decreased more than the A V shorten ing caused by increased frequency

In 3 patients tachycardia of over 100/minute without later effects and ventricular extrasystoles were observed the latter in 1 without simultaneous increase in frequency of sinus rhythm Subjectively the patients complained of a feeling of heat in the head general unrest heart palpitation and trembling but side effects were never severe In an ex tremely emotional hypertensive woman hyperventilation tetany appeared several minutes after administration of Isu

(4) S hw iz m d W hnsch 87 938 946 J ly 13 1957

tion is a disturbance from which the human heart rarely recovers spontaneously If not promptly terminated it is fatal. Ventricular fibrillation can be stopped by sending through the heart the discharge of a capacitor or an alternating current When the heart is already exposed in thoracotomy the open chest method with electrodes directly on the surface of the heart is preferable However during any other procedure the necessity for making the thoracotomy incision involves more trauma and loss of time

W B Kouwenhoven W R Milnor G G Knickerbocker and William R Chesnut[3] (Johns Hopkins Univ ) developed a method for defibrillating the heart through the closed chest

METHOD—The most reliable and effective method of ventricular defibrillation in dogs was a single application or burst of 60-cycle a c The dogs were resuscitated without heart massage after fibrillation had continued for up to 14 minutes The electrodes were soft sheet copper 4 6 in in diameter cemented on the surface of a ¼ in. thick plastic disk and mounted on hollow plastic tubes 6 in long 1 in in diameter that served as handles Connection to the copper electrode was made by an insulated conductor that passes through the tube To eliminate the possibility of accidental contact with the patient s body or the copper electrode another plastic guard was mounted on the tube 1 in above the electrode Electrode jelly was applied to the copper then held with pressure of 7 10 lb one on the suprasternal notch and the other in the midclavicular line at the level of the xiphoid

The current needed to defibrillate the ventricles ranged from 8 to 12 amp and voltage applied was 240 900 volts A potential of 480 volts open circuit proved sufficient and has been adopted as standard. The current was passed for ¼ second Should the initial application fail reapplication may be done some 15 20 seconds later

When ventricular fibrillation has been present for less than 2 minutes this method will save a high proportion of patients If it persists for more than 2 minutes defibrillation still is possible in most patients but often is followed by cardiac standstill and death unless thoracotomy and manual cardiac massage are carried out

Two patients were resuscitated One was a man aged 72 with Adams Stokes attacks due to ventricular fibrillation He had 10 such attacks successfully terminated over 4 days but after the 10th defibrillation the heart remained in standstill and he died The second patient was a girl aged 18 with Fallot s tetralogy in whom ventricular fibrillation developed during cardiac catheterization A defibrillating shock

(3) S rg ry 42 550 561 Sept mb 1957

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(4) S hw z. m d. W h h 87 938 946 J ly 13 1957

prel® but later in repeated studies and with use of pharmakon for months this was not observed Only 3 patients had continuous treatment of the carotid sinus syndrome with IPNA In 1 the daily dose was apparently too small to produce results 1 was not significantly helped and 1, aged 56 responded satisfactorily

Among the 11 patients with Adams Stokes syndrome IPNA relieved subjective symptoms completely in 10 and partially in 1 Attacks disappeared completely or appeared only seldom or under especially unfavorable conditions Objectively the principal finding was increase of auricular and automatic center frequency in total A V block Frequency increase of sinus nodes alone in 1 woman resulted in complete relief from symptoms although a 2 1 A V block continued Despite loss of every second beat sufficient ventricular frequency could be maintained

With total A V block in 4 patients with irreversible organic conditions the ventricular frequency was always accelerated by IPNA which cleared away the hypodynamic Adams Stokes symptoms A non fixed total A V block disappeared under IPNA treatment in 5 patients This type of block also responds to other drugs and is sometimes spontaneously reversible In these patients however spontaneous cessation of the Adams Stokes attacks was extremely unlikely since all were observed in a phase of progression of the condition In 1 a sinus rhythm with 1 1, 2 1 and 4 1 A V conduction was observed several times and IPNA never caused it to disappear Despite aleudrin therapy a definite total A V block appeared but the automatic center became stabilized at a favorable frequency and the patient became symptom free

These observations carried out over several months to a year in patients with Adams Stokes syndrome confirm the specific effect of IPNA in accelerating sinus frequency and stimulating substitute centers improving A V conduction time and decreasing A V conduction deficiency In contrast to the danger presented by epinephrine of stimulation of ventricular extrasystoles and extrasystolic tachycardia and of prefibrillatory and eventually even fibrillatory conditions IPNA appears never to predispose to these serious ectopic rhythms In 2 patients in whom the Adams Stokes attacks resulted from a disturbance of chamber autom [illegible]as well

as ventricular flutter i e of an extrasystolic ventricular tachycardia with total A V block IPNA showed no unfavorable effect but seemed to inhibit recurrence of the ventricular arrhythmia In contrast to epinephrine IPNA may be given without risk to patients with an Adams Stokes syndrome in whom an ECG is lacking to exclude a hyperdynamic disturbance In doubtful or combined disturbances the drug seems to provide the greatest margin of safety

The conclusion is that IPNA influences the function of the specific muscular system favorably with respect to conduction capacity and frequency of the automatic centers Effects differ according to pathologic anatomic basis in individual cases If damage of the conduction systems is relative the conduction deficiency decreases or eventually disappears If there is an absolute breakdown of the A V conduction system IPNA can only effect resuscitation of secondary or tertiary automatic centers

Dosage varies considerably in different situations and patients Sublingual administration is promptly effective Aleudrin can also be given perorally but the effect is delayed and less certain The single dose usually consists of 10 or 15 mg Isuprel® or 20 mg Aleudrin In some patients ½ or 1 tablet twice a day sufficed in others 7 tablets daily for months was necessary to maintain the initial result In threatening and especially resistant cases the dose/day can be greatly increased without serious risk One patient received 12 tablets of aleudrin for 5 days without side effects Other authors have reported doses of 14 24 tablets daily In severe cases high initial doses may be given—1 tablet at about hourly intervals Once the critical phase of an Adams Stokes syndrome has passed and regular heart action appears the dose should be decreased as soon as possible or withdrawn since in many patients certain loss of effect may ensue If dosage must be increased because of this undesirable side effects may appear that make continuance of effective treatment impossible In such instances IPNA is reserved only for acute attacks

Subcutaneous intramuscular or intravenous infusions can also be given until perlingual administration is again possible Dose of aleudrin is 1 cc of 1 500 solution intramuscularly of I oprel® 0 2 1 0 mg subcutaneously or 1 mg in 200 cc of 5% glucose solution intravenously (20 drops/minute)

prel® but later in repeated studies and with use of pharmakon for months this was not observed Only 3 patients had continuous treatment of the carotid sinus syndrome with IPNA In 1 the daily dose was apparently too small to produce results 1 was not significantly helped and 1 aged 56 responded satisfactorily

Among the 11 patients with Adams Stokes syndrome IPNA relieved subjective symptoms completely in 10 and partially in 1 Attacks disappeared completely or appeared only seldom or under especially unfavorable conditions Objectively the principal finding was increase of auricular and automatic center frequency in total A V block Frequency increase of sinus nodes alone in 1 woman resulted in complete relief from symptoms although a 2 1 A V block continued Despite loss of every second beat sufficient ventricular frequency could be maintained

With total A V block in 4 patients with irreversible organic conditions the ventricular frequency was always accelerated by IPNA which cleared away the hypodynamic Adams Stokes symptoms A non fixed total A V block disappeared under IPNA treatment in 5 patients This type of block also responds to other drugs and is sometimes spontaneously reversible In these patients however spontaneous cessation of the Adams Stokes attacks was extremely unlikely since all were observed in a phase of progression of the condition In 1 a sinus rhythm with 1 1 2 1 and 4 1 A V conduction was observed several times and IPNA never caused it to disappear Despite aleudrin therapy a definite total A V block appeared but the automatic center became stabilized at a favorable frequency and the patient became symptom free

These observations carried out over several months to a year in patients with Adams Stokes syndrome confirm the specific effect of IPNA in accelerating sinus frequency and stimulating substitute centers improving A V conduction time and decreasing A V conduction deficiency In contrast to the danger presented by epinephrine of stimulation of ventricular extrasystoles and extrasystolic tachycardia and of prefibrillatory and eventually even fibrillatory conditions IPNA appears never to predispose to these serious ectopic rhythms In 2 patients in whom the Adams Stokes attacks resulted from a disturbance of chamber automatism as well

as ventricular flutter i e of an extrasystolic ventricular tachycardia with total A V block IPNA showed no unfavor able effect but seemed to inhibit recurrence of the ventricu lar arrhythmia In contrast to epinephrine IPNA may be given without risk to patients with an Adams Stokes syn drome in whom an ECG is lacking to exclude a hyperdy namic disturbance In doubtful or combined disturbances the drug seems to provide the greatest margin of safety

The conclusion is that IPNA influences the function of the specific muscular system favorably with respect to conduc tion capacity and frequency of the automatic centers Effects differ according to pathologic anatomic basis in individual cases If damage of the conduction systems is relative the conduction deficiency decreases or eventually disappears If there is an absolute breakdown of the A V conduction sys tem IPNA can only effect resuscitation of secondary or tertiary automatic centers

Dosage varies considerably in different situations and pa tients Sublingual administration is promptly effective Aleu drin can also be given perorally but the effect is delayed and less certain The single dose usually consists of 10 or 15 mg Isuprel® or 20 mg Aleudrin In some patients ½ or 1 tablet twice a day sufficed in others 7 tablets daily for months was necessary to maintain the initial result In threatening and especially resistant cases the dose/day can be greatly in creased without serious risk One patient received 12 tablets of aleudrin for 5 days without side effects Other authors have reported doses of 14 24 tablets daily In severe cases high initial doses may be given —1 tablet at about hourly in tervals Once the critical phase of an Adams Stokes syn drome has passed and regular heart action appears the dose should be decreased as soon as possible or withdrawn since in many patients certain loss of effect may ensue If dosage must be increased because of this undesirable side effects may appear that make continuance of effective treatment impossible In such instances IPNA is reserved only for acute attacks

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1 1 000 epinephrine 10% calcium chloride and 1% procaine hydrochloride

In resuscitation the first step is to provide adequate ventilation with 100% oxygen accomplished initially with a tight fitting mask Later an endotracheal tube may be inserted Neo Synephrine® 0 2 cc (2 mg) with 1/60 gr (1 mg) atropine sulfate may be given intravenously with the infusion running rapidly during thoracotomy Compression through the intact diaphragm does not provide efficient circulation Standstill is about 9 times as frequent as ventricular fibrillation In either condition the heart should be compressed immediately against the posterior surface of the sternum 6 8 times If cardiac action is not resumed the ribs are spread to permit exposure of the pericardium defibrillation is accomplished by electric shock if indicated and drugs are accurately injected into the heart Effective manual systole 60-80/minute results in a palpable peripheral pulse and blood pressure of 80/60 mm Hg or more

In ventricular fibrillation manual systole should be used only long enough to restore adequate oxygen to the myocardium and brain after which electric shock is applied The electrodes 4 cm diameter for infants and children and 8 cm for adults are kept sterile and always ready for use One plate is placed behind the heart contacting the left ventricle near the apex the other over the right ventricle The plates are moistened with saline An initial shock of 110 volts is given for 0 1 second If unsuccessful 2 3 shocks may be tried in succession the voltage increased to 135 and the time to 0 5 second

If manual systole does not start the heart beating 0 5 cc of 1 1 000 epinephrine in 5 cc normal saline solution can be injected into the right ventricle 0 5 cc of 1 1 000 epinephrine in 9 5 cc of 1% procaine hydrochloride has been recommended by some As much as 8 cc of 1 1 000 epinephrine has been injected with subsequent recovery Isopropylnorepinephrine (Isuprel®) 0 02 mg has been recommended in standstill or heart block because it does not predispose to ventricular fibrillation

**Cardiac Asystole** arrest or standstill designates cessation of heart action It can occur without warning Untreated it terminates promptly in death The incidence of deaths in the

**Cardiac Arrest in Surgical Patients Prevention Recognition and Treatment** If circulation suddenly ceases manual systole electric shock or both with or without drug therapy are required to re establish effective circulation John L Keeley Arne E Schairer and James P Carroll[5] (Loyola Univ ) emphasize the 4 minute time limit within which circulation must be restored

One cardiac arrest has been calculated to occur in every 3 000 patients under anesthesia 1 in 1 000 elderly or poor risk patients and 1 in 5 000 young healthy good risk patients The emergency occurs in all hospitals large or small and the frequency is increasing because of the many types of surgery being done particularly among older patients

Almost without exception the cause of cardiac arrest is lack of oxygen in the vital tissues—the myocardium and central nervous system Airway ventilation exchange across the alveolar capillary network efficient circulation and blood volume and hemoglobin concentration are each essential Reflex stimulation may cause arrest In anesthetized patients the arrest is often associated with intubation extubation and tracheobronchial aspiration A surgeon capable by training and temperament to open the chest and compress the heart must be present when anesthesia is induced and extubation is being done

The routine use of monitors in every surgical patient is a valuable step in early diagnosis but it should not replace the constant and complete attention of a capable anesthetist An auditory monitor which may attract the attention of everyone when a sudden silence occurs is recommended In many instances early signs of sweating pallor cyanosis changes in cardiac rate or rhythm and altered respiratory pattern precede cardiac arrest

The most serious pitfall is delay in diagnosis Auscultation of the chest examination of eyegrounds or waiting for an electrocardiogram causes unnecessary and unwarranted delay Once cardiac arrest is suspected the chest must be opened immediately and a member of the team must count the time recording the time of each procedure and response to it A knife is the most important instrument A few hemostats a rib spreader syringes and needles should be available The drugs found most useful are solutions of

(5) S Cl North Am r c 38 55 74 F bru ry 1958

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**Cardiac Asystole** arrest or standstill designates cessation of heart action It can occur without warning Untreated it terminates promptly in death The incidence of deaths in the

operating room varies from 1 804 to 1 1858 anesthetics administered

Henry S Ruth Mary L Buckley and Kenneth K Keown[6] (Hahnemann Med College) list 10 conditions 2 or more of which are present before or at cardiac asystole (1) anemia and decreased circulating fluid (2) overdose of anesthetic agent (3) anxiety of the patient with increased outflow of epinephrine (4) increased level of serum carbon dioxide (5) cardiac and cardiovascular valvular diseases (6) hypoxia (7) administration of an undesirable drug or inaccurate dose of the correct drug (8) unrecognized administration of an unindicated and harmful compressed gas (9) cardiovascular effects induced by reflexes during anesthesia or surgery and (10) endocrine and metabolic disturbances

Cardiac standstill may occur at any time during anesthesia Most frequently it occurs at induction or emergence unless shock or surgical complications are present during the maintenance period

Protective measures require a well trained anesthesiologist thorough preanesthetic physical examination and evaluation with preoperative correction of any associated condition adequate preliminary medication and constant accurate evaluation of the status of anesthetized patients at all times When cardiac arrest is suspected no time should be lost in rechecking blood pressures that have been absent for 2 3 minutes When the carotid pulsations cannot be palpated cardiac arrest must be assumed No time should be spent in discussion with members of the operating team The most important factor for survival is the speed with which the chest is opened and effective compression of the heart begun When the chest is opened inspection reveals whether the heart is in complete standstill still contracting weakly or in ventricular fibrillation Usually the pericardium must also be incised

The most efficient ejection of blood results from rhythmic compression between the two hands at about 70 times/minute If continuous efficient contractions are not resumed 0 3 0 5 cc of 1 1000 epinephrine is given intravenously and repeated if necessary directly into the cardiac chamber If ventricular fibrillation develops it must be abolished and electric countershock is the only effective means Ordinary

(6) J A M A 164 831 836 J n 22 1957

house current 110 volts 60 c a c 6 10 amp applied through two oval metallic electrodes to opposite sides of the heart is effective in most cases When the heart is shocked to standstill rhythmic manual compression is again required

Manual respirations are necessary while the chest is open The breathing bag of the gas machine is rhythmically compressed 20 30 times a minute using 20 40 mm Hg during inspiration The carbon dioxide absorber must be in the circuit to control the carbon dioxide content of the respired gases

By use of these procedures 60% of the authors patients who had cardiac asystole have been saved The mortality rate of cardiac asystole can be decreased by prompt institution of definitive action

**Intravenous Drug Therapy of Stokes Adams Disease Effects of Sympathomimetic Amines on Ventricular Rhythmicity and Atrioventricular Conduction** Normally the ventricles respond to the sinoatrial pacemaker and the effects of drugs on ventricular pacemakers are masked by the effect produced on the primary pacemaker During treatment of 94 patients with Stokes Adams disease by external electric stimulation and defibrillation of the heart Paul M Zoll Arthur J Linenthal William Gibson Milton H Paul and Leona R Norman[7] (Boston) studied sympathomimetic drugs and 1M sodium lactate in 21 patients with complete absence of spontaneous ventricular activity During this time the only ventricular pacemaker was that supplied by the electronic external stimulator

Dilute solutions of epinephrine or isoproterenol (Isuprel®) intravenously were equally effective in arousing accelerating and maintaining intrinsic ventricular activity The effective dose 40 µg epinephrine (8 µg/minute for 5 minutes) was only a small fraction of the usual subcutaneous dose of 200 500 µg Isoproterenol was effective in doses of 5-43 µg/minute (average 12 µg) Levarterenol had a striking vasopressor effect but did not arouse ventricular pacemakers Once a stable pacemaker was present levarterenol increased the blood pressure reflexly slowed the sinoatrial rate and independently accelerated the rate of the idioventricular pacemaker Phenylephrine (Neo synephrine®) had only a vasopressor effect Limited observations

(7) C 1 t on 17 325 339 Ma ch 1958

of sodium lactate at the suggested intravenous rates of 7 30 ml/minute showed it to be less effective than epinephrine and isoproterenol in arousing and accelerating ventricular pacemakers

In choosing between epinephrine and isoproterenol the effectiveness must be compared with the risk of exciting ectopic ventricular activity The dose of each drug necessary varies from patient to patient and at different times in the same patient There is no striking difference in the cardiac effects of the two drugs Both require about equal amounts produce minor toxicity as excessive acceleration and premature ventricular beats which disappear promptly when the drug is stopped Epinephrine usually had a marked pressor effect whereas isoproterenol had no effect or lowered the pressure Isoproterenol usually accelerated the sinoatrial rate markedly whereas epinephrine had only slight effect If the first drug was ineffective or toxic the other was often successful

With intravenous drip the effects appear rapidly When the drip is stopped they rapidly disappear This moment to moment control allows greater safety but requires constant supervision and is impractical for long term administration after the emergency is corrected For prolonged acceleration and maintenance the drugs may be given by other routes

After a patient with Stokes Adams disease is resuscitated with the external electric pacemaker, stimulation should be stopped promptly to see if intrinsic ventricular activity has returned If this does not return within an hour and continuous external stimulation is required epinephrine or isoproterenol should be administered intravenously at 4 µg/minute (4 mg drug in 1 L of 5% dextrose in water at 15 drops/minute) In patients with high blood pressure isoproterenol is preferable because it has no pressor effect When blood pressure is normal or low epinephrine is the drug of choice The effects should be noted on an ECG during frequent short interruptions of electric stimulation Every few minutes the rate of infusion should be increased by increments of 4-8 µg/minute until a ventricular pacemaker is aroused or until frequent or multifocal ectopic beats ventricular rate over 50 beats/minute excessive ri e or fall in blood pressure or excessive stimulation of the c tral nerv

ous system occurs If the first drug fails or produces toxicity the other should be tried

When a ventricular pacemaker is aroused rate of drug administration should be adjusted until the idioventricular rate is 35-45/minute when the infusion should be gradually slowed and then stopped if this rate is maintained Oral epinephrine or sublingual isoproterenol may then be instituted for long term management

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## PHONOCARDIOGRAPHY AND AUSCULTATION

Incidental Systolic Murmurs from Hemodynamic Standpoint These systolic murmurs usually heard over the pulmonary area but sometimes at other precordial sites may occur in normal persons or in patients with hyperthyroidism anemia or fever with no evidence of cardiovascular disease They differ from so called functional systolic murmurs resulting from relative mitral valvular insufficiency or compression of the pulmonary artery Herbert Spitzbarth[8] (Univ of Mainz) noted these murmurs in 114 of 168 unselected medical patients aged 14 57 with no clinical x ray or ECG signs of cardiovascular disease None had a history indicative of heart disease

Incidence was highest among children and young adults to age 35 Measurements of heart rate blood pressure pulse pressure pulse rate peripheral resistance stroke volume cardiac output duration of isometric contraction and maximal systolic ejection revealed significant differences in patients with and without systolic murmurs those with incidental systolic murmurs having lower peripheral resistance greater stroke volume and wider pulse pressure Murmurs were most pronounced in patients with lowest peripheral resistance and greatest stroke volume Ratio of stroke volume to duration of maximal ejection was higher and duration *of isometric contraction was shorter in patients with* the murmurs The findings indicate that these patients have a shorter systole in relation to stroke volume than those without the murmur

The observations were confirmed essentially in 39 experi

(8) Deutsch med Wchschr 82 947 950 J 14 1957

ments on persons without cardiovascular disease in whom peripheral resistance and stroke volume were varied by exercise peripheral vasodilator or vasoconstrictor drugs

It is concluded that physiologic circulatory conditions characterized by low peripheral general resistance and relatively large stroke volume and anatomic peculiarities of the heart and cardiac vessels of children and young adults (expansion of the outflow tract of the heart chambers with passage into the large vessels, especially into the pulmonary artery) furnish the conditions for incidental systolic murmurs that are to be regarded as physiologic As with murmurs in hyperthyroidism anemia and fever and in similar circulatory conditions produced experimentally with dilated peripheral circulation these murmurs exist as 'tube outflow murmurs (Bondi) owing to turbulence in outflow from the right ventricle With extreme peripheral dilatation of the systemic circulation they may also occur in outflow from the left ventricle The murmurs exist only in the blood stream itself

The topographic site of the pulmonary valve in its relation to the anterior chest wall also enhances registrability of incidental systolic murmurs over this ostium That the circulatory speed in outflow from the ventricle is presumably greatest at the beginning of systole followed by gradual retardation explains the characteristic decreasing amplitude of the phonocardiographic picture In early childhood (to the 3d year) and in mature adulthood (35-40), incidental systolic murmurs are usually lacking because at these ages circulatory function displays higher peripheral resistance and smaller stroke volume

**Cardiovascular Sounds Clinical Aspects** are considered in a symposium[9] with Robert P Grant as moderator and Victor A McKusick as guest editor

*Some newer or poorly recognized auscultatory findings*— W Proctor Harvey Michael Corrado and Joseph Perloff (Washington, D C) summarize a miscellaneous group of clinical auscultatory findings Almost specific for ventricular tachycardia are extra sounds presumably due to wide splitting of the 1st and 2d sounds and gallop rhythm When these sounds are combined with the changing intensity of the 1st heart sound the slightly irregular ventricular rate and the

(9) Circulation 16 414-436 September 1957

lack of response to carotid sinus pressure ventricular tachycardia can be even more strongly suspected at the bedside

In mitral insufficiency the impact of the enlarged heart against the anterior chest wall in early diastole produces a sound Simultaneously the palpating hand feels a prominent impulse This sound—the ventricular knock —may be louder than even the 1st or 2d heart sound and is often misinterpreted as an opening snap or gallop

The systolic murmur of tricuspid incompetence is often misdiagnosed as mitral incompetence It may be grade III or IV or louder and be heard over the mitral as well as over the tricuspid area If the murmur is due to tricuspid incompetence its intensity is likely to increase with inspiration The murmur of mitral incompetence tends to decrease with inspiration

Textbooks emphasize the importance of the left lateral position in auscultation for the murmur of mitral stenosis However after the maximum apical impulse is found it is even more important to listen while the patient is turning to the left lateral position The typical diastolic murmur may be present for only 6-10 beats as the patient turns and then the murmur quickly wanes

*Discussion*—Aldo A Luisada (Chicago) states that the early diastolic sound in constrictive pericarditis amyloidosis and cardiac fibrosis is due to sudden checking of ventricular filling whether or not it is called a protodiastolic gallop

Harvey adds that in deciding whether a diastolic murmur at the left sternal border is a Graham Steell murmur or represents aortic regurgitation all the peripheral signs of the latter must be sought If the murmur is audible at all to the right of the sternum it indicates aortic insufficiency

*Splitting of heart sounds and classification of systolic murmurs*—Aubrey Leatham (London) states that splitting of the 1st and 2d heart sounds each into two major components can be recognized in most normal subjects and is due to slight asynchrony in onset and duration of left and right ventricular systole Of the two major components of the 1st sound mitral closure normally precedes tricuspid closure Delay of right sided events also will split the 2d sound in normal subjects Increase in right sided delay as in complete right bundle branch block is associated with abnor

mally wide splitting of the 1st sound best heard in the tricuspid area A split 1st sound is seldom obvious in left bundle branch block

A split pulmonic 2d sound during inspiration is normal in most children and young adults The earlier component is aortic valve closure and is the only one normally transmitted to the apex The later component is pulmonary valve closure and is heard only in the pulmonary area and immediately below it During inspiration the increased filling of the right ventricle selectively prolongs right ventricular systole

Abnormally wide splitting of the 2d sound even during expiration is caused by delay in pulmonary valve closure due to complete right bundle branch block or selective increase in right sided flow as in atrial septal defect or anomalous pulmonary venous return Pulmonary stenosis causes the greatest delay but the splitting may be difficult to hear since aortic closure may be obscured by the systolic murmur and the late pulmonary closure sound may be soft When pulmonary stenosis is associated with tetralogy of Fallot the pulmonary valve closure is rarely heard

Systolic murmurs are of two varieties The ejection murmur is due to flow of blood through the pulmonary or aortic valve It swells to a peak about midsystole and invariably finishes before the 2d sound Such aortic systolic murmurs may be transmitted to the apex The presence of a silent interval between the end of the murmur and the 2d sound is useful in differentiating this murmur from a mitral systolic murmur In aortic incompetence, a systolic murmur of similar shape results from increased stroke output across the deformed valve In pulmonary stenosis the murmur may last beyond and obscure the earlier aortic closure but always stops before the pulmonary closure sound Increased flow into the pulmonary artery is a frequent cause of pulmonary ejection systolic murmurs This may be due to atrial septal defect anomalous pulmonary venous return anemia, thyrotoxicosis pregnancy and increased stroke volume from slow rates as in complete heart block

The second variety of systolic murmur is the regurgitant due to mitral or tricuspid incompetence ventricular septal defect or patent ductus with left to right shunt These murmurs are always pansystolic

*Discussion*—Leatham points out that the loudness of the pulmonic 2d sound is not correlated with the severity of stenosis but varies with the anatomy of the chest dilatation of the pulmonary artery anatomy of the stenotic valve etc Delay in pulmonary valve closure is more reliable as an index of severity

*Clinical quantification of intensity of heart sounds and murmurs*—Eugene Lepeschkin (Burlington Vt) attributes confusion in grading systolic murmurs according to loudness to the use of the 6 grade system by some cardiologists and the 4 grade system by others Of 62 cardiologists polled 44 used 6 grades 8 used 4 grades and 10 did not use a system Grading a murmur is a highly individual process A more objective means is available in the amplifying electric stethoscope calibrated and modified to provide amplification or attenuation of +15 to —100 db

*Total anomalous pulmonary venous return and Ebstein s anomaly*—Patrick A Ongley (Boston) states that with complete transposition of the pulmonary veins pulmonary flow is much increased The murmurs heard are a systolic over the pulmonic area a middiastolic presystolic over the tricuspid area and frequently a continuous murmur or venous hum over the great veins

In Ebstein s anomaly (studied clinically in 10 patients with phonocardiograms of 6) the 1st sound is of normal intensity and is heard best at the apex The 2d sound is heard best at the lower left sternal border or the apex it is definitely diminished at the pulmonic area Despite marked right bundle branch block the 2d sound was either narrowly split or unsplit in 3 patients and was only normally split in 3 All patients had a systolic murmur of moderate intensity medium frequency and either decrescendo or crescendo decrescendo configuration A presystolic murmur was present in all and was quite intense in some

*Discussion*—Victor A McKusick (Baltimore) is impressed by the striking gallop occasionally double and resulting in quadruple rhythm in Ebstein s anomaly When this feature is heard in patients with cyanotic heart disease it should immediately suggest this malformation

*Editorial summary and conclusions*—Franklin D Johnston (Ann Arbor Mich) emphasizes the educational value of phonocardiography and points out two other ways in

which it is useful It permits precise time measurements and demonstrates sounds beyond perception of the ear It also allows documentation of the course of disease and the effects of therapy Johnston calls attention to the statements of William Dock in his Porter lecture The permanent objective records supplied by phonocardiograms are as valuable in managing heart disease as blood smears in leukemia chest films in pulmonary tuberculosis or electrocardiograms in coronary disease Perhaps their greatest value is in teaching us to be better doctors at the bedside and in the office and by making us less prone to error when the phonocardiogram is not available

► [This symposium contains a great deal of practical information. A half century ago many believed that the method of auscultation had been perfected and that its use by the experts of the time would never be exceeded in the future However this is not the case The development of phonocardiography as a widely used technic has led to an increased appreciation of the amount of practical information which can be obtained from careful listening to the heart In view of the increasing trend toward the substitution of instrumental for clinical methods this reversal is desirable. Just as the clinical recognition of the arrhythmias depended on the electrocardiogram so we are now learning from the phonocardiogram much more about practical auscultation —Ed ]

**Innocent (Functional) Cardiac Murmur in Children.** David H Fogel[1] (Yale Univ ) investigated the incidence and characteristics of the innocent or functional systolic murmur at a pediatric cardiac clinic The murmurs are of four types (1) One type is heard just below the nipple in the left parasternal line most commonly in children aged 2-6 It is characteristically a twanging sound between grades I and II in intensity less loud when the patient is erect of medium pitch and occupying the first half to two thirds of systole It gradually disappears in months or years (2) Next most common is a short blowing murmur grade I III over the base or pulmonic area transmitted parasternally and toward the apex The pulmonic 2d sound is always normal The murmur varies in intensity with change in position and is often accentuated by exercise It is most common in the adolescent (3) The cardiorespiratory murmur infrequent in children is usually heard at the apex over the heart and at the lung margins It is almost always systolic and varies with respiration Often it appears in midsystole distinctly separate from the 1st sound It begins and ends suddenly and is sharply localized It seems close to the ear of

(1) Pediat cs 19 793 800 May 1957

the examiner as a high pitched short squeal (4) The so called hemic murmur apparently due to anemia and poor papillary muscle tone usually resembles the innocent pul monic systolic murmur

The venous hum is common in childhood It is continuous with a diastolic accentuation heard to the right of the sternum as well as to the left and beneath the clavicle It is grade I III often high pitched and is louder when the pa tient is erect The diastolic component characteristically disappears when the patient is supine With rotation of the head or pressure over the neck veins the murmur decreases or disappears

Contrary to previous opinions most innocent systolic murmurs increase in intensity with exercise and frequently are well heard in the back A murmur cannot be classified as significant or insignificant on the basis of its intensity alone To discharge a patient as having an innocent systolic mur mur requiring no further cardiac follow up the clinical his tory must be negative the findings typical of an innocent systolic murmur the size and contour of the heart normal by roentgenogram and/or fluoroscopy and the ECG normal

► [Occasionally these functional murmurs may be indistinguishable from those associated with the milder degrees of pulmonic stenosis or of inter atrial or interventricular septal defect In such instances cardiac catheteri zation will not invariably establish the diagnosis because a shunt of mini mal degree may not be detectable by this procedure —Ed ]

**Confusion of Tricuspid Incompetence with Mitral Insuf ficiency—Pitfall in Selection of Patients for Mitral Sur gery** Five cases are reported by Donald P Schilder and W Proctor Harvey (Georgetown Univ ) In detecting sig nificant mitral insufficiency associated with mitral stenosis a combination of clinical criteria seems to achieve the great est percentage of correct diagnoses (1) a large dynamic left ventricle by physical examination FCG or x ray (2) an unusually large left atrium and (3) a loud apical systolic murmur The last criterion is the most important If the murmur is grade III and high pitched at the apex it usually means significant insufficiency Characteristically its inten sity diminishes on deep inspiration and it is transmitted best toward the left axilla and posterior lung base

A loud apical systolic murmur in itself however is not a contraindication to valvuloplasty if the patient is otherwise

(2) Am Heart J 54 352 367 S ptembe 1957

a suitable candidate Often it proves to be the transmitted murmur of tricuspid incompetence This lesion is not uncommon in rheumatic heart disease with mitral stenosis The classic clinical picture of pulsating veins and liver with right heart failure may be absent

The murmur of tricuspid incompetence varies It may be soft high pitched musical or even harsh In contrast to the murmur of mitral insufficiency it is often more superficial seeming closer to the ear It is heard best over the xiphoid area and along the lower left sternal border but if it is transmitted to the apex it may be confused with mitral insufficiency The classic murmur is inconstant, varying in intensity from day to day becoming louder after exercise generally loudest after long diastolic pauses varying with position and possibly disappearing if cardiac compensation improves It becomes louder on deep inspiration in contrast to the murmur of mitral insufficiency which becomes fainter

All 5 patients were initially suspected of having mitral insufficiency as well as mitral stenosis because of a loud apical systolic murmur Careful evaluation showed the murmur was that of tricuspid insufficiency Also the following features were usually present atrial fibrillation other physical evidence of tricuspid incompetence and severe right heart failure Functional pulmonary systolic murmurs were common and the murmur of pulmonary insufficiency was usually loud All patients proved to have tight mitral stenosis at surgery without significant insufficiency Surgery produced uniformly good results with lessened evidence of tricuspid insufficiency and lessening of the murmur

► [In the patient with undoubted evidence of mitral stenosis there are 4 common causes of systolic murmurs These include mitral insufficiency and aortic stenosis both of which are likely to be contraindications to surgical intervention In addition systolic murmurs may be due to tricuspid insufficiency or to dilatation of the pulmonary artery The 2 latter conditions are not contraindications and indeed may constitute additional reasons why mitral valvulotomy should be done Therefore the distinction between these various causes of systolic murmurs becomes of great practical significance It should be remembered that a given patient may present 2, 3 or rarely even all 4 of these murmurs —Ed.]

**Aortic Stenosis of No Physiologic Significance** The classic signs of aortic stenosis are a loud rough aortic systolic murmur transmitted to the neck a coarse aortic and carotid systolic thrill a diminished or absent aortic 2d sound a pulsus parvus et longus or an anacrotic pulse a n [illegible] pul e

pressure ECG evidence of left ventricular hypertrophy and roentgen evidence of enlargement of the left ventricle and calcification of the aortic valve However this classic picture is infrequent and aortic stenosis should be suspected if only one or two of these features are present

Assessment of the degree of aortic stenosis has become clinically important in evaluating patients for aortic valve surgery Catheterization of the left heart and determination of systolic pressure in the left ventricle compared with that in the aorta allows calculation of the size of the aortic valve orifice Ernest W Hancock William M Madison Jr Munro H Proctor Walter H Abelmann and George W B Starkey[3] (Boston) present data on 7 patients encountered during one year who had sufficient clinical evidence for aortic valve surgery to be seriously considered although atypical features were present in each Significant aortic stenosis was subsequently excluded by left sided catheterization in 5 and by autopsy in 2

All patients were men aged 51 67 hospitalized for severe cardiac symptoms attributable to left ventricular failure The murmur was typical in 5 and 2 had a thrill Six had a diminished or absent aortic 2d sound Phonocardiograms showed a symmetrical diamond shaped systolic murmur in the latter two thirds of systole None had an anacrotic pulse classic pulsus parvus et longus or carotid arterial thrill Roentgen examination indicated some degree of enlargement of the left ventricle in each Six had left ventricular hypertrophy by ECG In none was a pressure gradient demonstrable across the aortic valve Without catheterization of the left heart surgery would almost certainly have been undertaken in several of these patients

Aortic stenosis and chronic coronary artery disease may cause similar clinical syndromes of cardiac disease Functionally insignificant pathologic changes in the aortic valve may produce clinical signs indistinguishable from those of severe aortic stenosis Significant aortic stenosis is objectively established by catheterization of the left heart and this is indicated whenever surgery of aortic stenosis is considered and the degree of aortic stenosis is uncertain

► {With the increasing frequency of operative treatment of aort c stenosis a val d preoperative estimate of the degree of functional impairment has become of major importance. Many of these patients have coronary disease

(3) N w E gla d J M d 258 305 31 F b 13 1958

likewise and it frequently is well nigh impossible on the basis of clinical data alone to make the decision as to the relative importance of each *condition in causing cardiac disability* There is some evidence that the new technic of differentiating the pressure pulse as obtained from the root of the aorta may eliminate the necessity for catheterization of the left side of the heart. However at present this method even though somewhat *hazardous is the most certain way of determining the physiologic impor*tance of aortic stenosis in a given patient —Ed ]

**Auscultatory and Phonocardiographic Signs of Pulmonary Stenosis** were catalogued in 70 patients by Aubrey Leatham and David Weitzman[4] In patients without significant symptoms dilatation of the main pulmonary artery seemed greater by x ray The 1st sound was normal and followed by an extra sound 0 02 0 06 second later which gave the impression of wide splitting However, the extra sound was clicking in quality, and maximal at the pulmonary area and in expiration These features are characteristic of pulmonary ejection sound The 2d sound was widely split in expiration and the split increased during inspiration The *intensity of the pulmonic 2d sound was normal*

In moderate or severe pulmonary stenosis with intact ventricular septum right ventricular hypertrophy was evident *clinically and by ECG s Right ventricular systolic pressure* was 50-160 mm Hg The 1st sound was normal An ejection sound was heard in only 5 patients The 2d sound was ab*normally widely split and the pulmonary component was* soft and late The aortic component was often obscured in the loud systolic murmur in the pulmonary area The wide *splitting was due to prolongation of right ventricular sys*tole The pulmonary systolic murmur varied from moderately to very loud starting soon after the 1st sound and *tending to be long*

In all patients with the tetralogy of Fallot the ventricular septal defect with right to left shunt was demonstrated by *catheterization or angiocardiography All had cyanosis* and clinical and ECG evidence of right ventricular hypertrophy Pressures in the right ventricle ranged from 70 to 115 mm Hg and were equal to the systemic pressure in 18 patients The 1st sound was normal The 2d sound was always single before operation due entirely to aortic valve closure In 3 patients studied after surgery the pulmonic 2d sound became audible The greater reduction of pulmonary flow was

(4) Brit. Heart J 19 303 317 July 1

associated with a shorter and softer systolic murmur in some patients

Other causes for a pulmonary systolic murmur are increased pulmonary flow and dilatation of the pulmonary artery In atrial septal defect the increased pulmonary flow causes a short ejection systolic murmur similar to mild *pulmonary stenosis and wide splitting of the 2d heart sound* The pulmonary component of the 2d sound is of normal or increased intensity often transmitted to the apex and the splitting is unaltered by respiration and does not exceed 0 05 second In pulmonary hypertension there may be a soft or moderately loud ejection systolic murmur but the 2d sound is normally split the pulmonary component accentuated *and a pulmonary diastolic murmur frequently present*

The harsh pansystolic murmur of ventricular septal defect may closely resemble that of pulmonary stenosis but it is most intense at a lower site the 2d sound is normal in intensity and splitting Only in pulmonary stenosis is the pulmonary component of the 2d sound reduced in intensity or absent and separated from the aortic component by more than 0 05 *second*

**Obstructive and Relative Aortic Stenosis Differential Diagnosis by Phonocardiography** A systolic murmur over the 2d right intercostal space may be due to narrowing of the aortic valve (organic aortic stenosis) or dilatation of the ascending aorta (relative stenosis) Minimal narrowing due to fibrosis or calcification of the leaflets also may cause a loud murmur even though no obstruction results These types of stenosis can be differentiated by catheterization of the left heart or aorta or by studying the carotid tracing or aortic electrokymogram Christ Aravanis and Aldo A Luisada[5] (Chicago Med School) studied *70* cases to determine whether phonocardiography can be used in differential diagnosis

The amplitude of the murmur was without statistical significance confirming the known clinical fact that patients with relative stenosis may have murmurs as loud or louder than patients with organic stenosis The shape of the murmur by phonocardiography however was significantly different *in the two groups If the middle of systole is selected* as a point of division the murmur can be called early diamond when it occurs before this point and late diamond when it

(5) Am H rt J 54 32-41 J ly 1957

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occurs after Over 87% of the patients with relative stenosis had early diamond, over 66% with organic stenosis had late diamond In 90% of those with relative stenosis the murmur started immediately after the 1st sound and terminated 0 04-0 08 second before the 2d sound Less than half the patients with organic stenosis showed similar findings A large 2d sound was more typical of relative stenosis and a small 2d sound more typical of organic stenosis, but the difference was not clinically significant

Pulse tracings in the suprasternal notch and carotid arteries and electrokymograms of the aortic arch were significantly different in the two groups A slow rise flat top or anacrotic notch and multiple vibrations were important in organic, obstructive stenosis The large pul e rapid rise and smooth contour were characteristic of relative stenosis or nonobstructive minimal stenosis

**Stenosis of Branch of Pulmonary Artery Additional Cause of Continuous Murmurs Over Chest** Frederic Eldridge Arthur Selzer and Herbert Hultgren[6] (Stanford Univ ) report 3 cases of stenosis of the main branch of the pulmonary artery in 2 of which continuous murmurs were present Stenotic lesions distal to the pulmonary valve are rare The most likely causes are thrombosis or embolus or a congenital developmental defect There are no distinctive clinical signs of this lesion unless a continuous murmur is present Physiologic effects are not readily apparent unless a relationship to pulmonary hypertension can be demonstrated To detect such lesions during cardiac catheterization both branches of the pulmonary artery should be entered and withdrawal tracings recorded from each

Continuous ductus like murmurs are produced by this lesion only when stenosis is severe Several conditions must be present The channel must be narrowed and sufficient flow must be present through the constricted area to produce turbulence during both systole and diastole Both of these criteria are met in patent ductus arteriosus peripheral and pulmonary arteriovenous fistulas and in some of the more unusual arteriovenous communications In stenosis of the pulmonary artery branch the proximal pulmonary arterial bed acts as the reservoir under pressure

In acute experiments on dogs a special c clam

(6) Circulat on 15 865 874 J ne 1957

was placed around a large branch of the pulmonary artery with constriction done in stages Flow through the constriction was increased by completely occluding the right pulmonary artery When the constriction became severe a continuous murmur became audible

Surgery of patent ductus arteriosus now is so safe that all of these patients are operated on whether or not the lesions are dynamically significant The typical continuous murmur is considered pathognomonic for this lesion and few patients undergo special procedures to confirm the diagnosis The possibility of other conditions causing continuous murmurs over the thorax should constantly be kept in mind

Girl 7 had a loud slightly split 2d sound at the pulmonic area a grade III murmur filling systole over the left precordium and a loud continuous grade IV murmur at the right 2d intercostal space just medial to the midclavicular line well transmitted to the right axilla and back An ECG and chest x rays were compatible with right ventricular hypertrophy and increased pulmonary vascular flow A phonocardiogram confirmed the presence of a continuous murmur which was similar to that produced by the usual uncomplicated patent ductus Cardiac catheterization revealed high oxygen saturation in the superior vena cava arterial anoxemia moderate pulmonary hypertension and at least two sites of stenosis in the right main pulmonary artery Venous angiocardiography subsequently confirmed the presence of a total anomalous pulmonary venous return and moderate dilatation of the right pulmonary artery

► [Aside from patent ductus arteriosus one always has to think of a number of additional possible causes of a continuous murmur These include a communication between the aorta and pulmonary artery just above their sites of origin pulmonary arteriovenous fistula rupture of a sinus of Valsalva into the right atrium or right ventricle rupture of a syphilitic aneurysm of the aorta into the pulmonary artery and communications between coronary artery and coronary veins as well as the rare instances of fistula between the aorta and the superior vena cava —Ed ]

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## CARDIAC FAILURE

**Assessment of Exercise Capacity of Cardiac Patients** is important for proper advice to a patient about the level of effort that may be undertaken in work and sports C H Wyndham and J S Ward[7] (Johannesburg) studied the maximum exercise capacities in terms of liters of oxygen consumption/minute in patients with cardiac difficulties and in trained and untrained normal subjects

(7) C l t 16 384 393 S pt mbe 1957

occurs after Over 87% of the patients with relative stenosis had early diamond over 66% with organic stenosis had late diamond In 90% of those with relative stenosis the murmur started immediately after the 1st sound and terminated 0 04-0 08 second before the 2d sound Less than half the patients with organic stenosis showed similar findings A large 2d sound was more typical of relative stenosis and a small 2d sound more typical of organic stenosis but the difference was not clinically significant

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In acute experiments on dogs a special constricting clamp

(6) Circulation 15 865 874 June 1957

the terminal aspects of the last pregnancy in 2 patients In none was hypertension more than transient and none showed definite evidence of pre existing organic heart disease Six previously had syphilis

The initial symptoms of congestive failure developed within the first 3½ months post partum in 11 patients as late as 5 months post partum in 2 and in the last trimester in 2 In the last 2 symptoms disappeared at the delivery but reappeared 4-8 weeks later The earliest most consistent symptoms were cough that was worse at night and recurrent bouts of paroxysmal nocturnal dyspnea each noted in 11 patients In 7 of these symptoms preceded onset of exertional dyspnea orthopnea and hemoptysis Eight had chest pain 7 had gastrointestinal complaints and 3 had hematemesis Abdominal pain was reported by 6 and in 1 postmortem evidence showed that this was due to splenic and renal infarction Cerebral embolism with hemiplegia occurred in 2 and pulmonary embolism in 1

At time of admission labile predominantly diastolic hypertension was present in 14 of the 15 patients Auscultation of the heart revealed a gallop or triple rhythm in each precordial systolic murmur grade I III in 9 and accentuated pulmonic 2d sound in 12 Albuminuria was found in 11 but disappeared in all but 1 when compensation was restored Serial ECG s in 10 showed T wave inversion in multiple limb and precordial leads X ray study showed generalized enlargement of the cardiac shadow in all which persisted in the 5 patients who died In 7 the transverse diameter of the heart returned to normal limits in 3 16 weeks

Except for the 5 patients who died the symptoms of congestive heart failure improved in all after 8 60 days of hospitalization without specific therapy Before discharge blood pressures fell to normotensive levels but in the 1st year returned to hypertensive levels in 5 patients and by the end of the 4th year in 3 others Ten patients had 1 or more subsequent full term pregnancies in 6 exacerbation occurred resembling the original episode

Since 1937 15 autopsies have been reported The myocardium was soft flabby and dilated with ventricular mural thrombi especially near the apex Heart weights varied from 260 to 650 Gm The arteries were normal Histologic features included focal and diffuse myocardial degeneration occa

In trained men maximal effort on a bicycle ergometer proved that heart rate is a truly linear function of oxygen consumption Oxygen consumption at the maximum heart rates is correlated closely with the maximum aerobic levels determined by successive increments in the rate of work Limitation of effort is circulatory

Two women with cardiac abnormalities had approximately 50% of the normal maximum aerobic oxygen capacity and 2 men only 25% of normal The other 4 patients ranged from 50 to over 75% of normal In 2 patients the limitation of effort was ventilatory and not circulatory

At low levels of effort in normal men stroke volume heart rate and arteriovenous difference all contribute to the rate at which oxygen is made available to tissues Above a level of 1 5 L oxygen/minute (approximately six times resting level) only the heart rate and arteriovenous difference are involved Both increase as linear functions of oxygen consumption up to the maximum aerobic level

Eight patients with cardiac difficulties had ventilatory volumes/minute at three levels of oxygen consumption that were essentially the same as in normal subjects and therefore ventilatory function as in normal subjects was not the limiting factor to maximum possible oxygen consumption during severe exercise In 2 patients ventilatory response to exercise was abnormal Even mild effort induced larger than normal minute volumes which increased further as exercise was increased The primary cause was probably an inability to increase the cardiac output normally in relation to exercise

Assessment of the patient s maximum level of oxygen consumption is a useful objective index in choosing a safe level of work in determining the effect of therapy or surgery and in following the course of the disease

**Idiopathic Myocardial Failure in Last Trimester of Pregnancy and Puerperium** has been known for many years but was not adequately described until 1937 W R Meadows[8] (Cook County Hosp ) reports observations on 15 patients (13 Negroes) who were followed for 5 9 years together with autopsy findings in 4 of these Ages ranged from 22 to 44 years and the number of previous pregnancies from 1 to 10 A diagnosis of pre eclamptic toxemia had been made during

(8) Circulation 15 903 914 June, 1957

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sional hemorrhages and lymphocytic response all most prominent in the subendocardium

The cause of the endomyocardial lesions is unknown Evidence for a dietary deficiency is lacking These patients have degenerative heart disease of unknown cause Early the syndrome *is potentially reversible Bed rest should be prolonged* until after the heart size has returned to normal if this goal is achieved Although bed rest is sufficient in many others need digitalis About two thirds of these patients recover completely but the syndrome tends to recur with subsequent pregnancies

**Uncommon Myocardial Diseases** Noncoronary Cardiomyopathies are reviewed by Wallace Brigden[9] (London) Clinical and pathologic findings often fail to establish the cause in this group and they are labeled idiopathic Familial cardiomegaly is characterized by palpitation slight giddiness syncope cardiac enlargement triple rhythm arrhythmia and family history of premature sudden death Electrocardiograms usually show gross conduction defects At autopsy the heart is large giant fibers are noted with vacuolation and there is much fibrous tissue In several families there was associated ataxia muscle dystrophy or pseudohypertrophic muscular dystrophy When a second generation is affected the maternal parent appears to be responsible for transmission of the cardiomegaly It probably is inherited as a mendelian dominant and limited by being extremely lethal

Fibroelastosis of infancy and childhood probably is congenital and the evidence strongly suggests that it is different from adult endocardial sclerosis

Myocarditis may occur with most known infectious diseases and may be caused by viral bacterial rickettsial and protozoal infection Acute interstitial myocarditis often has been found at autopsy after sudden death Death sometimes occurs a few hours after onset of symptoms of chest pain shock and an abnormal ECG suggesting cardiac infarction Fiedler s name has been attached to myocarditis of weeks or months duration but such cases have no known common cause Chest pain *is common leukocytosis* sometimes is present pyrexia and raised sedimentation rate are infrequent and pericarditis is absent clinically and at autopsy The

(9) Lanc t 2 1 43 1249 Dec 21 1957

ECG ranges from T wave inversion to S T and QRS abnormalities

Isolated myocardial disease may be due to collagen disease The most acute are due to hypersensitivity e g serum sickness which has led to pericarditis myocarditis and even cardiac infarction In periarteritis nodosa local coronary arteritis causes areas of ischemic fibrosis In disseminated lupus erythematosus the myocardium is less commonly involved than is the endocardium or pericardium which almost always is affected Scleroderma sometimes is associated with widespread myocardial sclerosis

Systemic amyloidosis appears to be a disorder of protein metabolism Cardiac amyloid often is the major if not the only manifestation of primary amyloidosis The heart rarely is involved in secondary amyloidosis The greatest amount of amyloid is in the muscle particularly the subendocardial region The atria are nearly always affected and atrial arrhythmia is common Cardiac failure develops quietly Hoarseness slight dysphagia macroglossia and purpura are important clues and may indicate the diagnosis

Alcoholism is an important cause of nutritional heart disease Women are rarely affected Manifestations of nutritional heart disease are similar to those of beriberi Clinically it varies from hyperkinetic heart failure that responds to thiamine to hypokinetic heart failure that does not respond to vitamin therapy

*In treating heart failure in noncoronary cardiomyopathies* digitalis and mercurial diuretics usually produce good initial response Symptoms improve the venous pressure falls arterial pulse pressure increases slightly and edema diminishes There is little or no change in heart size triple rhythm persists and the ECG remains abnormal An episodic downhill course continues in most patients Death may occur suddenly and unexpectedly during recovery but usually follows progressive deterioration with low cardiac output No specific therapy is known Most patients with symptoms from isolated muscle disease whatever its nature died between 1 and 3½ years after the first symptoms of heart failure

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(9) Lancet 2 1243 1249 Dec 21 1957

able from beriberi heart failure All had mild congestive cardiac failure wide pulse pressures soft mitral systolic murmurs loud and split pulmonic 2d sounds and 1 had a protodiastolic sound The condition differed from beriberi in the immediate complete response to low thiamine diet and bed rest

The clinical features of the patients with noncardiac edema and the 3 patients who responded to low thiamine diet suggest that the same underlying cause is present—hypervolemia Idiopathic cardiac hypertrophy is a common finding at autopsy of South African natives Both ventricles are hypertrophied there is tendency to mural thrombosis and no specific lesion is found histologically The cause of the hypertrophy is unknown The condition in some way appears related to malnutrition possibly to a particular dietetic pattern Whether deficiency in vitamin $B_1$ can itself cause cardiac hypertrophy remains controversial

**Increased Aldosterone Secretion in Dogs with Right Sided Congestive Heart Failure and in Dogs with Thoracic Inferior Vena Cava Constriction** was demonstrated by James O Davis Maurice M Pechet Wilmot C Ball Jr and M Jay Goodkind Adrenocortical hormones have been known to be increased in the blood of patients with congestive heart failure and such patients also show increased urinary excretion of a sodium retaining compound Aldosterone excretion in the urine is inversely related to the excretion of sodium

Aldosterone is secreted in dogs with cardiac failure and in dogs with cava constriction considerably faster than in normal dogs Large amounts were present in adrenal vein blood but not in peripheral blood indicating that adrenal secretion was increased The rate of aldosterone excretion in the urine from dogs with heart failure or vena cava constriction was 2-6 µg daily and the estimated secretion into the blood was 560 780 µg daily In normal dogs urinary aldosterone could not be detected and the estimated rate of secretion into the blood was 130 µg daily Apparently only about 1% of secreted aldosterone is excreted in the urine of dogs Therefore studies of urinary excretion of aldosterone are of only limited value in estimating the rate of aldosterone secretion

(2) J Cl I t 36 689 694 M y 1957

ously venous pressure is high venous pulse has a characteristic wave triple rhythm is heard without murmurs ECG changes are diffuse and by x ray the heart is relatively immobile but clearly outlined

Acute Reversible Heart Failure in Africans is common and was investigated in 16 patients by H Grusin[1] (Univ of Witwatersrand) In all the cause was unknown In some patients it is due to some obvious cause such as acute nephritis anemia diphtheria or pulmonary embolism but in many the cause is obscure In early stages the heart failure can be reversed by adequate diet but usually it progresses to the chronic stage when the deficient home diet is resumed The 16 patients for years had an inadequate diet containing small quantities of animal protein and fat and high proportion of carbohydrate as maize Most were alcoholics who drank brandy and unmatured homemade brews All were confined to bed with weight and urinary output recorded daily and maintained for 5 10 days on a diet low in thiamine content but adequate in other respects If they were unimproved on this regime vitamin $B_1$ was added for 5 10 more days if they still were unresponsive digitalis and mercurial diuretics were given

Six patients lost 0 3 lb in 5 days on the low thiamine diet without change in physical signs In 5 9 days the physical signs and all edema disappeared and the pulse slowed Heart size returned to normal in 3 weeks Of 5 patients followed for 6 15 months 1 relapsed but none developed an enlarged heart

Ten patients responded completely to thiamine (beriberi heart disease) Three who had been ill with edema and breathlessness for 1 21 days did not respond to thiamine They had moderately severe heart failure with normal blood pressures no cyanosis valvular defect or any obvious cause for the failure Of these 3 2 lost most of the edema after 10 days of thiamine therapy but unlike patients with beriberi the elevated jugular venous pressure and hepatomegaly persisted disappearing only after 2 more weeks of bed rest The third patient did not improve until digitalis and mercurial diuretics were given

Three of the patients responded completely to the low thiamine diet Clinically their condition was indistinguish

(1) Circulation 16 735 July 1957

*ical manifestations Sodium chloride need not be given* orally nor hypertonic saline intravenously The presence of definite hyponatremia 100 126 mEq /L may represent far advanced heart failure with complications rather than the reverse Though the serum sodium concentration may be reduced total body sodium is considerably elevated Intracellular sodium is increased

Serum potassium is usually normal but total body stores are diminished indicating loss of intracellular potassium No consistent clinical benefit has followed potassium administration except when potassium depletion has been caused by therapeutic agents or complicating factors Potassium depletion appears to be entirely secondary to heart failure and not responsible for clinical symptoms Factors that alleviate heart failure lead to potassium repletion

Potassium may be depleted by anorexia nausea diarrhea intensive catharsis and various diuretic agents which eliminate potassium in excess especially if sodium has been restricted Potassium depletion thus induced may lead to intractable heart failure and digitalis toxicity Both improve more rapidly and more effectively if potassium is administered as well as digitalis discontinued When potassium depletion is severe enough to induce clinical manifestations drowsiness anorexia nausea muscular weakness in the extremities diminished or absent tendon reflexes or chronic ileus are induced Characteristic ECG abnormalities—depressed RS T segment prolonged Q T interval inverted T wave and a prominent or biphasic U wave—may confirm the diagnosis

Potassium salts should not be administered in the presence of renal insufficiency Oral medication is available as enteric tablets 1 2 Gm given 3 times a day or as a palatable mixture of potassium acetate bicarbonate and citrate (available commercially as Triplex) Each 5 ml contains 15 mEq potassium and 1 2 teaspoonfuls are given 3 times a day diluted in fruit juice If given intravenously the solution should contain 50 mEq in 500-1 000 ml of 5% glucose at a rate not exceeding 20 mEq /hour

Repeated mercurial diuresis at short intervals may induce (1) a proportionate loss of fluid and sodium (2) excretion of chloride in excess of sodium with potassium ammonium or both which leads to hypochloremia or (3) hyponatremia

Since cava obstruction has no primary effect on the heart or liver it is suggested that elevated venous pressure initiates the sequence of events which increases aldosterone secretion and subsequent renal retention of sodium The findings support the hypothesis that the sequence of events in cardiac edema is elevated venous pressure extravasation of fluid and electrolytes adrenocortical stimulation with consequent increased secretion of a sodium retaining hormone (aldosterone) and then sodium retention

**Fluid and Electrolyte Disturbances in Heart Failure and Their Treatment** are reviewed by Charles K. Friedberg[3] (Mount Sinai Hosp New York) Heart failure is related to sodium retention but the symptoms and signs of congestive failure are more related to an increase in the *quantity and* abnormal localization of body water The appearance or intensification of symptoms with weight gain and their prompt relief with diuresis and weight loss indicate these symptoms are determined by abnormal water retention *Most if not all* the excess body water is in the extracellular space characterized in advanced failure by edema and serous effusions In the presence of frank edema the extracellular fluid is usually at least twice normal Plasma volume probably also is increased in failure and tends to return to normal when failure is controlled However the increase is probably only 15 50% above normal

Water retention is secondary to an abnormal renal retention of sodium The benefits of salt restriction are obtained even when water intake is unrestricted The deleterious effects and abnormal retention of sodium chloride in congestive heart failure are due to the sodium and not the chloride ion Adequate sodium restriction is a foundation of modern effective treatment of congestive heart failure The degree of restriction must fit the impairment of sodium excretion Patients with mild congestive heart failure can usually tolerate 5 10 Gm sodium chloride daily without edema developing Severe heart failure can often be controlled only by extreme restriction to 200 mg sodium daily

The range of normal serum sodium is much wider than is generally recognized The commonly stated values of 140 or 143 mEq /l must not be interpreted literally Values between 130 and 140 are normal or at least do not cause clin

(3) C c lat on 16 437 460 S ptember 1957

Treatment is discontinuance of ammonium administration If the case is urgent isotonic 5% sodium bicarbonate or 1/6 M lactic acid should be given intravenously

The fundamental electrolyte disturbance in heart failure is abnormal retention of sodium With reasonable caution sodium restriction and mercurial diuresis can be fully used for maximum therapy When a patient with heart failure becomes refractory to treatment an electrolyte disturbance must be considered as one among many possible causes Hypertonic sodium chloride should not be hastily given until all the more frequent causes of refractoriness have been excluded and the presence of sodium depletion definitely established

The unfavorable clinical picture associated with electrolyte disturbances is usually not due to these disturbances Both are consequences of the inexorable progress of the serious underlying cardiac disease and its complications Careful reappraisal and improvement in therapy eliminating complications are more likely to correct these conditions than is intravenous administration of electrolytes designed to correct a chemical abnormality When the electrolytes are truly depleted benefit will be derived from their replacement

**Prevention of Hyponatremic Congestive Heart Failure** characterized clinically by extensive heart disease prolonged recurrent episodes of circulatory failure and intractable edema and chemically by considerable reductions in serum sodium and chloride with signs of increasing renal failure is facilitated by observance of certain principles according to Marvin F Levitt[4] (New York) The amount of salt restriction should be determined individually by the need for achieving negative salt and water balance In most intake of 2 3 Gm salt daily is adequate for maximum diuresis If further restriction is needed the potential ill effects of such a diet must be continually considered especially when renal disease also is present Extremely ill patients with cardiac disease should be cautioned about water intake because even moderate amounts may be more than they can handle Increasing thirst or sudden weight gain should be viewed with suspicion and water intake may have to be restricted to 1 000 1,200 cc /day

Diuretics should be used only as often as necessary and

(4) A M A A h I t M d 100 364-370 S pt mbe 1957

if oral sodium is restricted but chlorides or water are not

When mercurial diuretics are repeatedly given at brief intervals the plasma chloride may be markedly reduced with little or no reduction in plasma This excess is compensated by an increase in serum bicarbonate with resulting increased pH At the same time plasma potassium may be reduced because excessive potassium is excreted with chloride, which induces alkalosis The resulting serum electrolyte pattern is called hypochloremic alkalosis with hypokalemia It is likely to develop only if dietary restriction or anorexia prevents replacement of chloride or in severe failure This electrolyte disturbance due to mercurial diuresis may itself be responsible for lack of response to diuretics Chloride should be administered cautiously as dilute hydrochloric acid or ammonium chloride 6 9 Gm daily in divided doses It may be given intravenously in a 1 2% solution of 5% glucose if urgently needed The rate of administration must not exceed 1 Gm /hour or 10 Gm /day If hypokalemia is significant potassium should also be given

The hyponatremia of sodium depletion is characterized by relatively acute onset circulatory and renal insufficiency weakness muscle cramps apathy anorexia and somnolence The dilution type of hyponatremia develops more insidiously anorexia and apathy are early symptoms nausea and vomiting occur and the patient may be drowsy most of the day The serum electrolyte patterns in these two forms may be similar but a careful history of the development and the symptoms will usually differentiate them

When due to sodium depletion mild cases of hyponatremia are treated by increasing oral sodium intake If the case is urgent hypertonic sodium 300 ml of 3 5% solution is given intravenously In significant acidosis 5% sodium bicarbonate or 1/6 M sodium lactate should be given intravenously When hyponatremia is of the dilution type fluids should be restricted

Hyperchloremic acidosis is characterized by an elevated serum chloride concentration reduced bicarbonate and reduced pH Sodium is usually normal In heart failure this is usually due to prolonged administration of large doses of ammonium chloride or Diamox® Clinically the symptoms are anorexia nausea vomiting restlessness confusion lassitude or somnolence progressing to stupor and areflexia

in patients with congestive heart failure treated with digitalis

In each of 11 patients who were given 5 mg prednisone 4 times daily the effect was almost entirely favorable Five reported decreased dyspnea 3 of whom lost weight 5 who were well compensated had no untoward alteration in cardiac status and in only 1 was there questionable increase in exertional dyspnea associated with weight gain The 24-hour excretion of sodium was increased in 7 decreased in 2 and unchanged in 2 Potassium excretion was similarly affected

Prednisone can be used without hesitation for any desired therapeutic end in patients whose myocardial efficiency is reduced and may alleviate massive cardiac edema especially when response to mercurial and other diuretics is lost The mechanism of the beneficial effect in congestive heart failure is unknown but the most attractive hypothesis is that it counteracts production of aldosterone.

**Clinical and Laboratory Observations on Chlorothiazide (Diuril®) Orally Effective Nonmercurial Diuretic Agent** Chlorothiazide increases elimination of sodium chloride and water It is a nonmercurial orally effective agent with diuretic effects equal to or greater than any other available oral diuretic Ralph V Ford John H Moyer and Charles L Spurr[6] (Baylor Univ ) with the technical assistance of Ann Alexander Carol Marsh and Jean Gaffney studied effects of the drug in 10 men who were in compensated congestive heart failure and in unhydrated and hydrated dogs The effective dose lay between 1 and 2 Gm A dose of 4 Gm produced no toxicity but also showed no additional diuretic effect The drug is a potent inhibitor of renal tubular reabsorption of sodium and causes minimal excretion of bicarbonate but considerable excretion of chloride An oral dose has rapid onset within 2 hours and duration of action of less than 12 hours When given in repeated daily doses chlorthiazide is recurrently effective It produces no metabolic acidosis and has a high therapeutic index Oral administration is more effective than intravenous Administration at 12 hour intervals results in greater increase in sodium excretion than the same total dose given as a single dose/24 hours

(6) A.M.A. Arch Int Med. 100 582 596 October 1957

the effect measured by daily weights Greatest effect usually is achieved when the plasma and urine are temporarily acidified before use of the diuretic Ammonium chloride 6-10 Gm daily total 45-60 Gm or acetazoleamide 500 mg daily for 2 3 days may evoke extracellular acidosis In the particularly resistant the combination of acetazoleamide and ammonium chloride may be necessary Extreme caution is necessary when renal disease is present because severe acidosis and coma may be induced ✓

Every patient whose kidneys retain sodium whose salt intake is reduced for prolonged periods and who is subjected to repeated diuretics should be maintained with potassium supplements 60 100 mEq as organic salts for 3-4 days after each diuretic or after every 7 10 days Such oral dose is safe in the absence of rising plasma urea concentration and when urine output is adequate Daily weights are most important Plasma urea or creatinine concentrations may forewarn of failing renal function plasma bicarbonate and chloride concentrations may forewarn of impending alkalosis Increasing bicarbonate concentration may prove more valuable in detecting this trend than any other measurement

Once hyponatremic edema develops treatment usually is fruitless Management of this clinical picture depends primarily on prevention by understanding the technics of the negative salt and water balance Correcting the hyponatremia in an edematous cardiac patient is paradoxic and use of hypertonic salt to increase electrolyte concentration generally provides no clinical benefit

**Use of Prednisone in Congestive Heart Failure** The adrenal cortical steroids lead to retention of sodium and water and excretion of potassium all of which may be detrimental in patients whose myocardium is already failing Corticoids have been considered contraindicated in established cardiac failure However several cases recently have been reported *in which excessive edema in patients with congestive* heart failure and nephrosis responded to corticotropin and corticoids

In an attempt to clarify this problem Leonard B Gutner John B Moses Sidney Dann and Herbert S Kupperman[5] (New York Univ Bellevue Med Center) studied the effect of prednisone on sodium potassium and water excretion

(5) Am J M Sc 234 31 36 S pt mber 1957

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(5) Am. J M Sc 234 81 286 Sept mbe 1957

in 3 patients by intravenous infusion of 600 mg disodium salt of EDTA a chelating agent that binds and inactivates serum calcium This dose is well within the limits of toxicity As much as 3 Gm may be given safely within 20 minutes inducing only hypocalcemia accompanying ECG changes transitory fine muscular tremor and acral numbness

Action of EDTA is prompt and the drug is safe for treating digitalis toxicity

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## MISCELLANEOUS

**Staphylococci Antibiotics and Endocarditis** According to a recent report staphylococcic infections appear more prevalent more virulent and more unavoidable than 25 years ago in the prepenicillin era In hospitals these infections have almost assumed the status of an environmental disease Maxwell Finland[8] (Harvard Med School) calls attention to a survey made in 1956 which showed that 181 of 1 172 patients occupying beds at a given time in Boston City Hospital had some type of staphylococcic infection Nearly two thirds had acquired the infections in the hospital

During 1955 Micrococcus pyogenes var aureus was grown from blood cultures of 302 patients 127 (42%) of whom died Nonhemolytic strains were isolated from blood of another 90 patients 51 (57%) of whom died Micrococcus albus was cultured from blood of 384 patients and 70 (18%) died Among 914 autopsies in which satisfactory blood cultures were made there were 86 in which hemolytic Staphylococcus aureus was grown from cardiac blood or the spleen or both At 47 other autopsies similar organisms were obtained in blood cultures from vegetations on the cardiac valves brains meninges peritoneum pericardium bones and joints During this same year beta hemolytic streptococci were grown from blood cultures of only 4 patients enterococci from 21 and pneumococci from 78 Gram negative bacilli were grown from blood cultures of 222 patients This incidence represents considerable reversal of the ratio found before introduction of the sulfonamides and penicillin Then the hemolytic streptococcus was the com

(8) C lation 15 641 645 M y 1957

The predominant electrolyte excretion after chlorothiazide is in sodium and chloride The effect on potassium and bicarbonate is smaller in the presence of an alkaline urine A dose of about 500 mg chlorothiazide is roughly equivalent to 40 mg Neohydrin® (4 tablets) and about twice as potent as Diamox® A dose of slightly more than 1 Gm is equivalent to 1 cc Mercuhydrin® given intramuscularly

An average dose of chlorothiazide that is effective in controlling chronic congestive heart failure is 500 mg given twice daily Clinical experience over 3 months indicates that this drug is effective in replacing current oral and parenteral diuretic agents in managing chronic congestive heart failure

**Treatment of Digitalis Toxicity by Chelation of Serum Calcium** was successful in 5 patients treated by Richard S Gubner and Harold Kallman [7] Increased use of digitalis glycosides in place of cruder preparations has accentuated the problem of toxicity Arrhythmias often are the first sign of overdosage and gastrointestinal symptoms may be inconspicuous or lacking Concurrent use of diuretics increases excretion of potassium and contributes to the problem because potassium depletion and calcium excess enhance the toxic effects of digitalis Conversely potassium administration and calcium deficit have prevented or abolished arrhythmias induced by digitalis However oral potassium salts are not well tolerated and are inadequate for managing serious arrhythmias Prompt therapy is required but intravenous potassium is dangerous Hypocalcemia may be rapidly induced by intravenous sodium citrate or the chelating agent ethylene diamine tetra acetic acid (EDTA) and by using the magnesium salt of EDTA serum magnesium is elevated simultaneously

Digitalis and calcium have synergistic effects The inotropic action of digitalis depends on presence of calcium Chelation of serum calcium abolishes digitalis induced supraventricular and ventricular arrhythmias of which the commonest is paroxysmal atrial tachycardia with varying block that may masquerade as ventricular tachycardia or ventricular extrasystoles Digitalis toxicity is dangerous not only because fatal arrhythmias may develop but because heart failure may be greatly aggravated

Arrhythmias due to digitalis toxicity were ended promptly

(7) Am J M Sc 234 136-144 Aug 1957

hypertensive encephalopathy localized cerebrovascular disease and reflex hyperventilation states

Classic chronic postural hypotension is uncommon It is usually associated with organic central nervous system disease When the subject is erect the blood pressure falls abruptly quickly followed by syncope It is more common in the morning on arising than in the afternoon Syncope from a hypersensitive carotid sinus is most likely in sitting or standing position and may cause sinus bradycardia partial or complete heart block extrasystoles atrial tachycardia flutter and fibrillation nodal tachycardia ventricular tachycardia and fibrillation and cardiac arrest

Drug syncope can be induced by morphine which diminishes or abolishes important reflex activity in the aortic arch and carotid sinus Nitroglycerin alcohol the newer hypotensive drugs atropine sulfate Mecholyl® quinidine sulfate and procaine amide may also induce syncope through their peripheral vasodilatory action

In the tetralogy of Fallot children assume the characteristic knee chest or squatting position after exercise and cyanosis and dyspnea are strikingly relieved The position increases the volume of venous blood return to the heart and increases the oxygen saturation of the mixed venous blood Patients who have hypertension due to pheochromocytoma frequently show a significant drop in blood pressure and a tachycardia as they stand The usual patient with hypertension does not

Posture in man is maintained by a delicate balance of complicated reflexes A disturbance is reflected in a wide variety of circulatory manifestations Unless the physician is alert to the importance of posture influences many diagnoses will be overlooked or misinterpreted

**Clinical Examination of Heart** is now more important than ever since early detection of significant heart disease must start in the physician s office before ECG s x rays or exercise tolerance tests John R Blake and Walter T Goodale[1] (Harvard Med School) review some signs which are often neglected on inspection and palpation especially the timing of heart ounds and murmurs

In minimal or combined ventricular hypertrophy the ECG and x ray are much less reliable than simple physical

(1) M Cl N rth Am 41 1215 1228 S pt mbe 1957

monest cause of sepsis and pneumococcic bacteremias were relatively more frequent

The seriousness of the problem is reflected in recent reports of staphylococcic endocarditis and its treatment Resistance to antibiotics may be decisive in the fatal outcome The more favorable reports are those in which treatment was intensive with many antibiotics The importance of using combined therapy with agents to each of which the causative organism is at least moderately susceptible cannot be overemphasized The chance of resistance developing to both antibiotics is small Treatment must be continuous and prolonged Predetermined combinations of antimicrobials in fixed ratios should be scrupulously avoided Combinations containing penicillin cannot be relied on in actual therapy to have any effect against penicillin resistant strains beyond that which can be expected from the other constituents of the combination unless the amount of penicillin itself has some inhibitory effect

With respect to tetracycline and its analogues oxytetracycline and chlortetracycline strains of bacteria resistant to one may be considered resistant to the others The same is true of erythromycin and the related antibiotics carbomycin oleandomycin and spiramycin

Despite all the effective agents currently available and their intensive use in various combinations the over all recovery rate in staphylococcic endocarditis in recent years is still close to 50%—no better than results in 1952 Perhaps new and effective agents will become available to which the staphylococcus will not become resistant

**Role of Posture in Cardiovascular Disease** Jacob J Silverman and Siegfried Salomon[9] (Staten Island N Y ) discuss postural syndromes of interest to the cardiologist Vasodepressor syncope simple fainting is common and usually benign but may be fatal if recumbency is not quickly established Many cardiovascular situations may precipitate an attack peripheral circulatory failure ventricular rates over 180 emboli or infarction prolonged recumbency and convalescence aortic valvular disease sudden visceral catastrophes ordinary venesection or paracentesis loss of blood electrolyte disturbances and dehydration hypoglycemia

(9) A I t Med. 4 59 0 J ly 1957

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The murmurs of mitral and tricuspid regurgitation start with the 1st sound and extend throughout systole at the same intensity or slightly decrescendo They are high pitched and blowing Murmurs of aortic and pulmonary ste nosis are harsh begin slightly after the 1st sound rise to a peak near midsystole and taper off before the 2d sound They are well transmitted to the neck and over the precordium The systolic murmur of ventricular septal defect is usually plateau best heard in the 3d or 4th left interspace and poorly *transmitted to the neck*

Diastolic murmurs almost invariably indicate structural heart disease The Austin Flint murmur is a presystolic murmur at the apex in patients with aortic regurgitation identical by auscultation with the presystolic murmur of mitral stenosis The Graham Steell murmur due to pulmo nary regurgitation is maximal along the left sternal border and has characteristics similar to the murmur of aortic re gurgitation In combined mitral stenosis and regurgitation a snapping 1st sound and an opening snap strongly favor predominant mitral stenosis A well developed 3d heart sound strongly favors predominant mitral regurgitation

[Careful palpation of the precordium is a much neglected procedure Frequently it is the single most reliable indication of hypertrophy of the left or right ventricle Diffusely increased pulsations over the whole pre cordium may be the result of right ventricular hypertrophy of increased cardiac output due to such conditions as anemia or thyrotoxicosis or even to simple anxiety or of infarction of the interventricular septum An ex aggerated localized apex thrust may be due to left ventricular hypertrophy to an anatomic or functional aneurysm of the apex after myocardial in farction or to a temporary bulge of the apex due to angina in which case the prominent apical bulge will disappear after nitroglycerin therapy Pa tients with marked right ventricular hypertrophy may rarely have an ex aggerated apex thrust In such patients the right ventricle appears to make up the apex This may lead to confu ion with left ventricular hypertrophy Occasionally a patient with aortic valve lesion may have pronounced pul sations over the whole precordium and this may be confused with right ventricular hypertrophy Howev r careful palpation remains ne of the most rewarding of all methods of examining the heart —Ed ]

**Syndrome of Hyperventilation** Mario Enrique Forteza[2] (Cleveland Clinic) reports 150 cases It has been estimated that the hyperventilation syndrome i e respiratory alka losis caused by psychogenic hyperpnea with no evidence of organic disease related to the symptoms occurs in 5 10% of patients seen in general medical centers or by internists

(2) M d n B A 17 132 161 M y 1957

examination Left ventricular hypertrophy appears as a forceful localized apical systolic thrust often accompanied by systolic retraction of the skin in the interspace just above and medial to the apex The thrust lifts the fingers and is obviously increased in force Right ventricular hypertrophy produces a diffuse lifting impulse along the left sternal border frequently associated with systolic retraction at the apex

The normal jugular pulse is seen best when the patient is lying with the head slightly elevated Giant *a* waves are due to powerful right atrial contraction and increased resistance to right ventricular filling as in severe pulmonary stenosis marked pulmonary hypertension and tricuspid stenosis and atresia A thrill over the carotid artery is most commonly a transmitted murmur from the aortic or pulmonary valve It may also be due to rapid flow through tortuous sclerotic vessels or through an enlarged overactive thyroid

In auscultation of the heart one must concentrate selectively on each specific event in the cardiac cycle in all pertinent areas If timing of the sounds is difficult it should be remembered that the carotid pulse immediately follows the 1st sound It marks the onset of ventricular systole and is produced by closure of the mitral and tricuspid valves A split 1st sound is a normal finding The loudest 1st sound is produced when the P R interval is short and the leaflets wide open when the ventricles contract The 2d heart sound is due to aortic and pulmonary valve closure In the 2d and 3d left interspaces it is made up of both aortic and pulmonary components but in the 2d right interspaces it comprises only the aortic Pulmonary valve closure is best heard in the 3d left intercostal space This sound is normally split the 1st component being aortic closure and the 2d pulmonic During inspiration splitting becomes wider Right bundle branch block pulmonary stenosis and atrial septal defect cause wider splitting of the 2d sound at the base Pulmonary hypertension accentuates the sound of valve closure but narrows the degree of splitting

Gallop rhythm is the cadence produced by the addition of an extra sound Protodiastolic and presystolic gallop sounds are basically much the same as the normal 3d and 4th heart sounds The opening snap of the mitral valve is characteristic of mitral valvular disease It occurs perceptibl later

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(2) Medicina B enos Ai 17 13 161 M y 1957

The syndrome occurs at all ages though most patients (77%) are adults over age 30 In 82% first manifestations of the syndrome appeared between ages 20 and 49 In some symptoms had been present for over 20 years Ratio of women to men was 3 2 Hyperventilation is always associated with anxiety states and the immediate cause is recognizable in about a third of the cases Many patients had had psychosomatic or psychiatric illnesses

Psychogenic hyperventilation is one of several factors e g salicylate intoxication lesions of the central nervous system anoxia excessive ammonia in the blood thyrotoxicosis fever infection high altitude etc that may cause respiratory alkalosis by increasing alveolar ventilation Hyperventilation within a short time produces pronounced fall in tension of plasma carbon dioxide which precipitates a series of electrolytic and metabolic disturbances Signs of neuromuscular hyperexcitability and EEG changes and changes in cerebral blood flow are noted Vasodilatation and consequent hypotension are attributed to local changes in electrolytes and pH of the blood and not to the nervous system because fall in blood pressure is observed in the forearm of patients with loss of autonomic nerve function produced by surgery or disease or block of the branchial plexus

Changes in the ECG may be seen in some healthy patients subjected to voluntary hyperventilation or in patients with psychogenic hyperventilation without cardiac pathology These changes consist of inversion of the T wave or depression of the S T segment with marked flattening of the T wave Changes have also been described in the QRS complex and prolongation of the Q T interval These changes may be seen in one or all leads and disappear when the subject recovers spontaneously from hypocapnia or breathes a gaseous mixture containing 5% carbon dioxide

The main symptoms of the syndrome are hyperpnea of variable degree decrease in level of consciousness (sometimes loss of consciousness) due to cerebral vasoconstriction paresthesias chest pains muscular contractions and spasms anxiety lassitude tremors headaches tinnitus palpitations tachycardia aerophagia nausea and vomiting choking sensation and blurred vision The three clinical types are acute or in intermittent crises chronic and mixed

There were 46 men and 61 women with the acute type 4 men and 14 women with the chronic type and 9 men and 16 women with the mixed type In the last type the constant relatively mild symptoms are interrupted by acute manifestations precipitated by situations causing anxiety

Diagnosis is based on history normal physical examination and when necessary in differential diagnosis additional negative special studies and reproduction of symptoms by voluntary hyperventilation which also has great therapeutic value Differential diagnosis includes coronary heart disease pulmonary hypertension of various origins pulmonary embolism anterior chest wall syndrome cardiac dyspnea pheochromocytoma syncope neurocirculatory asthenia epilepsy arterial vertebral compression syndrome internal ear diseases hyperthyroidism hypoglycemia and hypothyroidism Besides reproduction of symptoms by voluntary forced respiration treatment involves superficial psychotherapy instruction on avoidance of hyperpnea and pharmacologic agents that reduce anxiety

► [This disorder is not only common in patients who have no organic disease but is a frequent cause of symptoms in patients who have organic cardiac disease which in itself is asymptomatic. In such subjects the anxiety often iatrogenically induced may lead to hyperventilation and the symptoms of this syndrome are frequently confused with those due to organic heart disease Such confusion is common in patients but not rare on the part of physicians

One of the most valuable means of therapy consists in producing the symptoms over and over again by having the patient hyperventilate and explaining to the patient how the manifestations can be quickly overcome by voluntarily restricting the breathing When the patient learns that he or more commonly she can turn the symptoms on and off at will the anxiety is likely to be much improved —Ed ]

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## PULMONARY CIRCULATION

**Pachydermoperiostosis (Idiopathic Osteoarthropathy)** Clubbing of the fingers occasionally is seen in healthy persons In some patients in whom no evidence of intrathoracic or cardiac disease has been found gross clubbing of the fingers has been associated with enlarged extremities thickened skin particularly over the face and a periosteal reaction in the long bones In 25% these features are heredi

tary J H Angel[3] (Postgrad Med School London) reports 3 cases

The condition affects males predominantly At puberty the hands and feet enlarge rapidly for 3-4 years The skin of the face forehead scalp hands and feet is thickened The upper eyelids are often thickened and the face is drawn into thick folds appearing lined and creased The most prominent folds are in the cheeks and on the forehead and the nasolabial folds are greatly exaggerated Hypersecretion of sebaceous glands makes the skin greasy this may be associated with acne

Enlargement of the extremities may lead to a diagnosis of acromegaly Usually only the hands and feet are involved but occasionally the forearms wrists elbows and legs up to midthigh are affected The ends of the fingers and toes show drumstick enlargement and the nails are curved and beaked in all planes resembling a watchglass in contour

The characteristic bony changes are deposition of periosteal new bone most often seen in long bones Articular surfaces are always spared The changes are earliest and best seen in the distal third of the leg and forearm The new bone is laid down on the surface of the old cortex and gradually becomes fused with it so there is no clear line of demarcation

The syndrome resembles hypertrophic osteoarthropathy but a primary lesion is absent Prognosis for life is excellent Patients with joint involvement may be disabled Treatment is of little avail Tarsorrhaphy may be required in those with considerable hypertrophy of the eyelids If sweating is prominent sympathectomy will improve this The etiology is unknown

**Diffuse Bilateral Pulmonary Edema Associated with Unilobar Miliary Pulmonary Embolization in the Dog** A marked disproportion has been observed between the amount of pulmonary vascular bed directly affected by multiple small emboli and the extraordinary severity of the sequelae encountered Donald Singer Charles Hesser Ruth Pick and Louis N Katz[4] (Michael Reese Hosp ) studied the sequence of events after embolization by producing emboli in dogs by intravenous injection of starch granules

(3) B it M J 2 789 792 O t. 5 1957
(4) C culat on R 6 4 9 J uary 1958

Distribution of starch in the lungs was primarily a function of the site of injection In 10 dogs receiving 1 Gm into the left pulmonary arterial wedge position almost all the starch was on the side of injection most commonly in capillaries but also in clumps in arterioles Injection into a branch of the left pulmonary artery produced a similar unilobar spread in 19 of 24 animals but 5 had bilateral distribution with large numbers of granules in the several lobes Such unilobar miliary emboli in almost all instances caused a confluent pulmonary infarct and bilateral severe pulmonary edema In those animals in which a pulmonary infarct did not develop the edema in the noninjected lobes was minimal or absent

Previous studies showed that pretreatment of the animals with a variety of antiadrenergic and antihistaminic compounds often markedly diminishes or completely eliminates edema formation in the noninjected lobes but has little effect on the edema of the injected lobe The accumulated data suggest that the starch has a dual mechanism (1) a local action on the site surrounding the parenchyma and vasculature producing the infarction and (2) a distant action involving some neural or neurohumoral mechanism responsible for edema in the remainder of the lung The injected starch is entirely or at least overwhelmingly localized to the injection site The number of granules found in other lobes is insufficient to produce the edema by any direct action of their own

The association of localized pulmonary infarction with generalized pulmonary edema formation poses the question of a possible role of the infarction as the trigger mechanism for distant edema formation

**Interrelationship between Cor Pulmonale Capillary Bed Restriction and Diffusion Insufficiency for Oxygen in the Lung** Single organs do not exist in a vacuum but are affected by changes elsewhere in the body This is especially true in the integral relationship between cardiac and pulmonary function Peter C Luchsinger Kenneth M Moser Albert Buhlmann and P H Rossier[5] (Univ of Zurich) emphasize certain facets of cardiopulmonary study that may prove useful in evaluating several groups of cardiac patients

Increased pulmonary arteriolar resistance may be func

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tional thus reversible or organic and irreversible The functional form is due to alveolar hypoventilation such as may be produced by emphysema bronchial asthma kyphoscoliosis and paralysis of the respiratory muscles The resulting hypoventilation leads to reduction of alveolar oxygen tension and elevation of alveolar carbon dioxide tension These changes initiate mechanisms that increase pulmonary vascular resistance and pulmonary hypertension ensues Alleviation of the hypoventilation reverses pulmonary hypertension

The organic form results from pronounced decrease in the cross sectional area of the pulmonary capillary bed due to extensive pulmonary resection pulmonary emboli tuberculosis sarcoidosis Hamman Rich syndrome silicosis and beryllıosis Despite normal ventilation organic restriction of the pulmonary vascular bed results in increased and fixed pulmonary resistance Restriction of the capillary bed is not only a major cause of cor pulmonale but also simultaneously causes diffusion insufficiency for oxygen in the lung

Ten patients with pulmonary diffusion insufficiency for oxygen due to various clinical disorders were studied Each had a wide alveoloarterial oxygen gradient at rest that increased to pathologic values with exercise Cardiac catheterization and pulmonary function studies showed normal or increased alveolar ventilation normal mean pulmonary capillary pressure abnormally high pulmonary arteriolar resistance at rest or with exercise (in contrast to normal decrease in resistance with exercise) an elevated alveoloarterial oxygen tension gradient at rest and a greatly increased gradient with exercise and elevated levels of right ventricular work at rest and abnormally high levels with exercise rising in exponential fashion with increase in cardiac output

The rise of pulmonary artery pressure with increased cardiac output with fixed vascular resistance implies an increase in velocity of blood flow through the capillary bed The widening of the alveoloarterial oxygen gradient with exercise in absence of a shunt is characteristic of diffusion insufficiency Development of such a defect indicates that perfusion of the alveolar bed occurs so rapidly that contact time between alveolus and capillary is insufficient for equili

bration between alveolar oxygen tension and capillary blood Right ventricular work increases simultaneously

Thus two factors can cause a diffusion problem one is anatomic the thickened membrane across which diffusion is hampered the other is physiologic in that time of contact between alveolar blood and the alveolus is too short to allow equilibration

Diffusion is not a pure membrane problem Diffusion insufficiency and cor pulmonale are closely related Pulmonary artery pressure and right ventricular work are uniformly elevated in persons with diffusion insufficiency at rest Any further increase in pulmonary blood flow leads to an exponential rise in right ventricular work Diffusion insufficiency at rest implies fixed pulmonary arteriolar resistance pulmonary hypertension and increased levels of right ventricular work When diffusion insufficiency is absent at rest but develops with exercise the level of exercise at which pulmonary hypertension and increased right ventricular work will develop can be accurately defined When diffusion is normal at rest and during considerable exercise the pulmonary vascular bed has retained its expansile capacity and is not a fixed resistance

**Pulmonary and Systemic Vascular Response to Continuous Infusion of 5 Hydroxytryptamine (Serotonin) in Dog** The pulmonary circulation has been considered to be unresponsive to most factors affecting the systemic vasculature such as exercise anoxia and drugs Serotonin has a hypertensive effect on the pulmonary vessels of isolated perfused lungs *Abraham M Rudolph and Milton H Paul*[6] (Harvard Med School) infused this compound continuously into a peripheral vein of 8 dogs Pulmonary artery pressure rose rapidly two to four times normal levels and returned to normal levels slowly after infusion was stopped Systemic arterial pressure also rose but the rise was not maintained The pressure slowly fell though infusion was continued to hypotensive levels Pressures returned to normal 8 30 minutes after infusion was stopped Left auricular pressure was not altered significantly Cardiac output rose 10 50% above control levels and the heart rate was increased during serotonin infusion in each case

Pulmonary vascular resistance increased two to threefold

(6) Am J Phy 1 189 263 68 M y 1957

with slow infusions and fivefold with more rapid infusions reaching one third to one half the calculated systemic vascular resistance Systemic vascular resistance dropped markedly during infusion Arterial hypoxia was noted in each case but no appreciable change in pulmonary vascular resistance was induced by breathing pure oxygen

These studies revealed a significant increase in cardiac output as measured by the Fick and dye dilution methods The marked pulmonary hypertension produced by serotonin was *especially interesting since most other mechanisms have* had no effect The rise occurred immediately after injection of the compound into the pulmonary artery and was probably the result of a direct local effect on small pulmonary vessels

Serotonin has a powerful vasoconstrictor effect on the pulmonary vessels The hemodynamic and respiratory changes of pulmonary embolism may be related to serotonin released from clotted blood Serotonin may also play a role in the production of pulmonary hypertension in congenital heart disease associated with shunting of blood from the systemic to the pulmonary circulation Pulmonary hypertension occurs more commonly with ventricular septal defect and patent ductus arteriosus in which turbulence is marked This turbulence may cause platelet disruption releasing serotonin into the pulmonary circulation

**Primary Pulmonary Hypertension** Pulmonary hypertension may accompany various disorders which can be identified clinically or by catheterization of the heart In some cases however no cause is obvious and such cases have been considered primary pulmonary hypertension Hiroshi Kuida *Gustave J Dammin Florence W Haynes* Elliot Rapaport and Lewis Dexter[7] (Harvard Med School) studied 4 cases in which pulmonary hypertension was later proved by autopsy to be primary All 4 patients were young women Two had had no pregnancies and 2 had had multiple pregnancies Symptoms had persisted 3½ 12 years and consisted of prominent dyspnea on exertion syncope cyanotic episodes chest pain cough and edema Only 1 had detectable *cyanosis* and clubbing Of the 2 with heart murmurs 1 had a nonspecific precordial systolic murmur and the other had two distinct diastolic murmurs indistinguishable from

(7) Am. J Med 23 166-182 A gu t, 1957

mitral stenosis and pulmonic regurgitation Hematocrits were slightly to moderately elevated in each The ECG s were characteristic of right ventricular hypertrophy Chest x rays revealed uniform prominence of the main pulmonary artery with right ventricular enlargement One had typical hilar dance

By cardiac catheterization the most striking abnormali *ties in all 4 patients were the elevated pulmonary artery* pressures and calculated vascular resistance Arterial oxygen saturations were below normal in all Cardiac minute out puts were reduced Two patients had elevated mean right atrial and right ventricular diastolic pressures consistent with right ventricular failure Valid pulmonary capil lary wedge pressures obtained in only 2 were low normal

The ultimate physiologic defect causing precapillary pul monary hypertension whether primary or secondary is the increased resistance to blood flow across the pulmonary bed This intrapulmonary stenosis resides in the smaller pulmo nary arteries proximal to the capillary bed A high pressure gradient can be demonstrated between the pulmonary artery and the pulmonary artery wedge pressures

Catheterization can exclude most cases secondary to con genital heart disease or obstructing lesions in the left heart by demonstrating left to right shunts or elevated pulmonary capillary pressures Differentiation from recurrent silent pulmonary emboli is impossible In some cases of patent duc tus arteriosus aortic pulmonary fenestration and ventricu lar septal defect if the shunt is entirely right to left because of the pulmonary hypertension cardiac catheterization may *be erroneously interpreted as showing primary pulmonary* hypertension

No single feature or combination of features in either the clinical or catheterization evaluation can be considered char acteristic of primary pulmonary hypertension Diagnosis may be suggested by painstakingly excluding all factors which could cause secondary pulmonary hypertension Al though definitive diagnosis depends on autopsy even here the exact mechanism may be difficult to define Only two lesions were common to all 4 patients arteriosclerosis and arteriolosclerosis of the pulmonary arteries Both can be re garded as the sequelae of pulmonary hypertension The sys temic vessels were not involved

**Neurologic Manifestations of Chronic Pulmonary Insufficiency** Many different chronic pulmonary diseases may give rise to dyspnea cyanosis heart failure polycythemia papilledema and coma Often the neurologic symptoms dominate the clinical picture and the underlying pulmonary disease may be overlooked or considered to be unrelated Recognition of the cause will preclude the need for arteriography or ventriculography Measures that correct the hypercapnia hypoxia cardiac failure and polycythemia may completely resolve the neurologic disorder Frank K Austen Miriam W Carmichael and Raymond D Adams[8] (Massachusetts Gen l Hosp ) report 4 cases and attempt to clarify the relation between neurologic findings and the altered cardiopulmonary physiology

The main components of the syndrome are symptoms and signs of pulmonary and cardiac failure headache papilledema impaired consciousness and tremor and twitching of the extremities Chronic pulmonary insufficiency was the underlying disorder in each of the 4 cases Left and right sided congestive heart failure was present The headache may be generalized frontal or occipital intense persistent and of steady aching type It usually occurs at night or in the early morning The papilledema cannot be distinguished from that associated with other causes of increased intracranial pressure and varies from slight blurring of the disk margins to choking with venous congestion and hemorrhages The principal complaint of the family and employers against the patients was that they were extremely drowsy and often fell asleep while at work eating or conversing They were forgetful irritable and easily confused

On examination the patients were drowsy and inattentive and consciousness varied from slight reduction in attention to stupor to coma Tremor and twitching of the extremities were conspicuous findings The former had all the characteristics of an action tremor being present whenever the muscles of the forearm and hands were contracted A coarse twitching movement occurred whenever the muscles were activated and maintained in contraction The twitchings were arrhythmic and asynchronous identical to those in hepatic coma At the time of the twitch the normal continuous pattern of action potential was interrupted in

(8) N w E gland J Med. 257 5 9 590 Sept 26 1957

flexor and extensor muscles This distinguishes it from myoclonus The EEG s showed abundant activity in the slower frequency ranges in all leads with prominent theta and delta waves Alpha activity tended to be slow and of increased amplitude The abnormalities could be completely reversed when the pulmonary defect was corrected

Papilledema is most likely to appear in the patient with moderate pulmonary insufficiency regardless of type in whom heart failure with pulmonary congestion and increased venous pressure acutely develops Aggravation of the existing hypoxia and hypercapnia leads to edema and congestion of the brain which in turn causes the papilledema

Elevated carbon dioxide tension probably is the main factor in development of drowsiness and impaired consciousness With chronically elevated carbon dioxide tension the respiratory center loses its responsiveness to changes in carbon dioxide tension and the principal stimulus to respiration is hypoxia acting on the aortic and carotid body chemoreceptors When oxygen was administered hypoventilation increased and consciousness was further impaired This deterioration with relief of hypoxia but increased hypercapnia indicates the importance of carbon dioxide retention in producing altered consciousness

Therapy was directed toward restoring cardiac and pulmonary compensation digitalis mercurial diuretics and salt restriction being used When polycythemia was marked reduction in blood volume by phlebotomy was useful Hyperventilation chemotherapy and bronchodilators were used to combat pulmonary failure

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## CERFBRAL CIRCULATION

**Order and Disorder in Cerebral Circulation** are discussed by Russell Brain[9] (London) The blood supply to the brain depends directly on systemic blood pressure and inversely on resistance by the cerebral vessels Normally these are mutually adjusted to maintain the optimum supply of blood to the brain Anatomically the circle of Willis stands on the four legs of the two carotid and two vertebral arteries Its

[9] Lancet 2 857 862 N 1957

branches the anterior middle and posterior cerebral arteries intercommunicate where their cortical territories meet The internal carotid and basilar artery share the bood supply to each cerebral hemisphere in such a way that there is normally no interchange of blood between them Similarly the flow from the internal carotid arteries meets in the middle of the anterior communicating artery When one artery is occluded its territory is supplied by the other

The circle of Willis guarantees that whatever the position of the head relative to gravity and to the trunk and however the relative flow through either carotid or vertebral artery may vary for the moment these variations are always compensated by the freest possible anastomoses before the brain is reached Collateral circulation exists at three levels the supply to the circle of Willis the circle itself and the level at which the territories of the anterior middle and posterior cerebral arteries meet A patient with atheromatous narrowing of the internal carotid and vertebral arteries on one side may remain free from symptoms until the internal carotid becomes completely occluded when infarction occurs in the ipsilateral cerebral and cerebellar hemispheres The carotico vertebral system should be regarded as a unity

Variations in systemic blood pressure affect blood flow through the brain When atheromatous narrowing of the cerebral artery is present a fall in pressure may cause transitory symptoms of cerebral ischemia or permanent symptoms due to infarction Confinement to bed surgery myocardial infarction or blood volume changes produced by mercurial diuretics may precipitate a stroke in a patient with atheroma

The symptoms of transitory ischemia of one cerebral hemisphere resulting from atheroma of the internal carotid artery are familiar By use of a measured pressure on the eye it may be shown that blood pressure in the central retinal artery is lower on the affected than on the normal side since the supply comes from the internal carotid The cerebrospinal fluid is likely to have an increase in protein and cells Abnormalities in the EEG may be found over some part of the affected hemispheres Palpation of the carotids should always be carried out Cerebral angiography may be valuable

Once a stroke has occurred recovery depends on the collateral circulation which can be established The patient

should move his sound limbs while in bed and sit out of bed as soon as possible It is doubtful whether any vasodilator drug dilates the cerebral vessels in fact such an agent may impair cerebral blood flow by lowering the systemic blood pressure Hypotensive drugs should be used with caution It is difficult to see how sympathetic block can directly improve the blood flow through the brain since there is no *important vasoconstrictor nerve supply to the cerebral vessels* in man Anticoagulants can most plausibly be used in patients with cerebral atheroma who have transitory ischemic attacks especially if the vertebrobasilar system is involved since the prognosis in such cases is always grave Arterial surgery is a promising method of treatment particularly if the lesion is localized just above the bifurcation of the common carotid

**Clinical Aspects of Cerebral Vascular Insufficiency** are evaluated by Eliot Corday and Sanford F Rothenberg[1] (Los Angeles) Transient cerebral vascular disturbances resulting from widespread cerebral ischemia are usually manifested as syncope or grand mal seizures The manifestations of a more localized cerebral vascular disturbance vary depending on the area affected and include transient hemiplegia hemianopsia monoplegia aphasia paresthesia and localized convulsive patterns A patient may show the same sign or symptom repeatedly with complete recovery after each episode

These little strokes are due to localized cerebral ischemia Because of sudden onset and rapid disappearance without residua they have been attributed to cerebral vascular spasm However no vasomotor apparatus has been shown in cerebral vessels beyond the circle of Willis and cerebral vasospasm is high improbable These clinical manifestations cannot be explained on the basis of small emboli or thrombi because the transient attacks disappear too rapidly Absorption of hemorrhage and edema and recanalization of a clot take much longer it is improbable that all emboli in a patient can be expected to dislodge themselves and move on It also is difficult to believe that emboli would repeatedly strike only one particular area and make it more vulnerable than other areas

The most adequate explanation for these clinical phenom

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ena is that the cerebral arteries are narrowed Acute vascular insufficiency results when systemic arterial blood pressure is inadequate or cardiac output is impaired Although often transient and reversible it may cause permanent brain damage if not promptly corrected The vascular insufficiency may involve the entire brain or may be localized When generalized such manifestations as syncope and grand mal seizures may occur When localized focal manifestations result Reduction in systemic blood pressure may cause focal cerebral ischemia by decreasing blood flow through an already narrowed cerebral artery especially when the systemic pressure falls enough so that collateral circulation to the affected cerebral region becomes inadequate The cerebral changes are reversed when the blood pressure is restored

Symptoms and signs of cerebral vascular insufficiency are similar to those of an acute cerebral thrombosis Clinical conditions in which cerebral vascular insufficiency may occur include shock—hemorrhagic coronary (acute myocardial infarction) anaphylactic insulin and traumatic hypotension due to antihypertensive drugs postsympathectomy hypersensitive carotid sinus postural hypotension hypotensive episodes of reflex origin cardiac arrhythmias surgical procedures anesthetics congestive heart failure pulmonary hypertension thermal vasodilatation Valsalva maneuver gravitational states angiography after injection of contrast material hypothermia sleep and pulmonary embolism

In the patient with known cerebral arterial disease every effort must be made to avoid an excessive drop in systemic blood pressure or reduction in cardiac output Antihypertensive drugs and anesthesia must be used with great care Steam baths vasodepressor procedures stimulation of the carotid sinus straining at stool violent coughing and sleeping in an erect position should be avoided After the cause of cerebral vascular insufficiency is determined corrective therapy should be promptly instituted Blood loss must be promptly replaced arrhythmias corrected and shock counteracted Careful nursing prophylaxis against infections early ambulation and physical rehabilitation will be indicated

**Carotid Artery Occlusion and Its Diagnosis by Ophthalmodynamometry** are discussed by Francis A Wood and

James F Toole[2] (Univ of Pennsylvania) Hemiplegia present sooner or later in 80% of patients often is preceded by premonitory transient hemiparesis monoparesis aphasia dysphasia paresthesias alterations in consciousness monocular blindness focal or general seizures and headaches The tendency for these transient symptoms to recur and recede should lead to suspicion of carotid involvement It is assumed but not proved that the premonitory symptoms and signs correspond to stenosis of the artery and hemiplegia to complete occlusion Intermittent symptoms often reflect decreased systemic blood pressure from whatever cause Many patients may have sudden onset of hemiplegia without premonitory signs mimicking the more common type of cerebral vascular accident Primary carotid disease should be considered in differential diagnosis of all cerebral vascular symptomatology Confirmation of the diagnosis depends on special examination In the past the only method has been carotid arteriography

Ophthalmodynamometry is a means for measuring pressure in the central artery of the retina This is a branch of the ophthalmic artery which is the first sizable branch of the internal carotid artery Diminution in pressure in the carotid artery due to occlusion or stenosis at any point proximal to the origin of the ophthalmic artery must of necessity be transmitted to the central artery of the retina This is the basis for the transient occasionally permanent monocular blindness in carotid occlusion The rich collateral circulation prevents blindness in most patients

When intraocular tension is increased to the point where it equals diastolic pressure in the central retinal artery the vessel begins to pulsate and pulsation can easily be observed by the ophthalmoscope When pressure is further increased pulsation ceases and the vessel collapses Pressure is applied to the globe by a simple spring loaded dynamometer that is manipulated with one hand while the ophthalmoscope is held with the other The unit is calibrated in grams In normal persons the required extraocular pressure is similar in the two eyes The pupils may be dilated with a mydriatic and examined while the patient is seated or supine Application of pressure is not painful but a drop of local anesthetic will eliminate blinking and reflex movement

(2) J A M A 165 1264 1270 N 9 195

Measurement of pressure in the central artery of the retina by ophthalmodynamometry is safe and practical at the bed side Significantly lower pressure in one eye is a reliable in dication of occlusion of the carotid artery on the same side In 5 patients with carotid occlusion as proved by surgical exploration or arteriography the method was useful accu rately reflecting occlusion in all and the restored patency postoperatively in 2

Sources of error in interpreting measurements may be in creased intraocular tension other intrinsic ocular disease previous cataract extraction stenosis or occlusion of the innominate artery or of the orifices of the great vessels and papilledema

Contraindications to ophthalmodynamometry although infrequent are a history or findings suggesting glaucoma funduscopic evidence of retinal artery branch occlusion high myopia peripheral choroiditis and retinal disease that pre disposes to retinal detachment

**Electroencephalographic Evaluation of Treatment in Obstructive Disease of Basilar and Carotid Arteries** Athero sclerosis of the carotid and basilar arteries is a common cause of neurologic disability John S Meyer Walter Wegner Charles A Kane and Oscar M Reinmuth[3] (Boston) tested the cerebral collateral circulation before and after treatment in 90 patients with occlusive disease of these vessels The EEG ECG and blood pressure readings were taken simul taneously during tilting on a tilt table and during alternate compression of the carotid arteries in the neck

Diagnosis was confirmed by arteriography or inspection of the affected vessel at operation in 11 patients at autopsy in 5 and by the typical EEG changes during tilting or carot id compression in 37 In the other 37 diagnosis was based solely on clinical signs and symptoms Average period of clinical observation was 16 months

Of 23 patients who were not treated *17%* improved spon taneously but most of these were patients who had recov ered from an infarct in the distribution of the carotid artery In general patients with repeated attacks of transient neu rologic deficit became worse either because the attacks in creased in frequency or because cerebral infarction resulted eventually within 2 years *72%* were severely disabled or

(3) N r l gy 7 765 776 N mber 1957

dead During the observation period there was a progressive increase in the EEG abnormalities induced by postural tilting and carotid compression

Of 41 patients treated with Dicumarol® 75% were significantly improved Of the 4 deaths in the group 3 occurred within 4 weeks of discontinuing treatment The patients who improved the most had vascular insufficiency without infarction If cerebral infarction had been sustained before treatment no improvement was noted Tests on 19 patients showed that EEG abnormalities were no longer obtained by tilting or carotid compression in 7 were less marked in 10 and were unchanged in 2 The EEG evidence thus supported the clinical impression that cerebral circulation in this group was benefited in some way by anticoagulation therapy Ephedrine therapy was less effective than anticoagulation but did result in improvement

Of 5 patients who had surgery 1 had an excellent result from side to side anastomosis of the external to the internal carotid artery with return of motor and sensory function in the arm and leg 1 improved for the first 4 weeks but carotid pulsation was no longer palpable and hemiplegia returned and 3 were found to have obstructed internal carotid arteries throughout the length of the artery

When patients breathed oxygen or 7% carbon dioxide and oxygen the EEG abnormality was less pronounced Tight abdominal binders and elastic stockings to reduce postural hypotension decreased the abnormalities in 3 of the 4 patients tested

Since local cerebral blood flow depends on systemic blood pressure the first therapeutic consideration should be maintenance of adequate cardiac output Transient reduction may precipitate cerebrovascular insufficiency Heart failure when present should be treated with digitalis and arrhythmias converted Elastic stockings and firm abdominal support minimize postural hypotension but are uncomfortable for continuous wear and often are discarded Anticoagulant therapy appears to improve cerebral collateral circulation but the mechanism is obscure Benefit probably is not due to recanalization of the occluded vessel alone Surgery of the internal carotid artery in the neck occasionally is justified The ideal candidate should have severe stenosis rather

than complete occlusion and be free from advanced heart disease

Certain precipitating factors appeared causally related to onset of transient ischemic episodes These included blood loss digitalis poisoning straining at stool postural hypo tension use of hypotensive drugs an unusually heavy meal and cardiac dysrhythmia The factor common to all of these is transient reduction in cardiac output

**Prognosis of Subarachnoid Hemorrhage Comparison between Patients with Verified Aneurysms and Patients with Normal Angiograms** was made by G af Bjorkesten and Henry Troupp[4] (Helsinki) The prognosis in subarachnoid hemorrhage is grave About a third of the patients die from the first bleeding and another third from recurrent hemorrhage a considerable number of survivors are incapacitated

Of 101 patients studied 40 had an intracranial aneurysm confirmed by angiography or at autopsy and typical clinical symptoms and signs of subarachnoid hemorrhage The other 61 patients had subarachnoid hemorrhage verified by lumbar puncture but normal bilateral carotid angiograms No patient was treated surgically

*Unconsciousness and/or major neurologic signs* such as hemiplegia hemiparesis convulsions or long standing mental symptoms were noted in 24 of the 40 patients who had a demonstrated intracranial aneurysm and in 39 of the 61 without a demonstrable aneurysm The incidence of hypertension was 13 of 38 (in 2 of the 40 no blood pressure record was available) and 12 of 61 respectively

*In the aneurysm series the mortality rate was more than ten times as high as in the no aneurysm series* Of the total 25 deaths 22 occurred within the 1st year and 15 within the first 2 months There was no correlation between unconsciousness and the chances for survival nor did the prognosis seem influenced by the presence of major neurologic signs the condition of the patient during the attack or the presence or absence of hypertension

Aneurysms of the internal carotid artery had the worst prognosis those of the anterior cerebral and anterior communicating arteries the best At follow up patients who had had no demonstrable aneurysm were in better health and

(4) J Ne ro g 14 434 441 J ly 1957

had the better working capacity than those in whom an aneurysm had been demonstrated

The prognosis in subarachnoid hemorrhage is not uniform It differs with presence or absence of a demonstrable aneurysm and its location Even if the source of bleeding in a patient with no demonstrable aneurysm is unknown the prognosis is better than when an aneurysm is found and not operated on

**Cerebral Collateral Circulation II Production of Cerebral Infarction by Ischemic Anoxia and Its Reversibility in Early Stages** Remarkable functional recovery may occur after thrombosis and insufficiency of the major cerebral vessels In fact recurrent intermittent symptoms characterize the syndromes of insufficiency of the basilar and carotid arteries In most such transient paralyses onset of symptoms is due to a fall in systolic blood pressure thus decreasing blood supply to an area already compromised by stenosis or occlusion of its major tributary Recovery may follow resumption of adequate cardiac output and sometimes occurs though cardiac output remains low In these cases collateral circulation may have adjusted to the insufficiency

D Denny Brown and John S Meyer[5] (Harvard Med School) in studies on monkey cerebral circulation found that cortical ischemia can proceed to the point at which the electrocorticogram fails and an injury potential is seen yet recovery may be rapid and apparently complete without evidence of damage to vessels Occlusion of the middle cerebral artery in the healthy monkey with normal blood pressure has surprisingly little effect on the area of brain supplied Large anastomoses with the anterior and posterior cerebral arteries provide collateral circulation for the cortex To induce immediate tissue damage the blood pressure must be drastically reduced Prolonged or repeated occlusion of the proximal portion of the main trunk of the middle cerebral artery then regularly causes varying degrees of neuron and vascular injury

Continued occlusion of the middle cerebral artery or its rupture in the presence of low blood pressure results in progressive clumping of the column of blood and eventual blocking of arteries and veins of all sizes with a well defined demarcation between infarcted and relatively anemic brain

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In the infarcted zone all blood flow ceases except rarely a sluggish flow continues in a few arteries and veins Lowering of the blood pressure or breathing nitrogen causes an increase in the area of infarction These changes occur with circulatory collapse with complete failure of collateral supply a circumstance rare in vascular disease

If the blood pressure is less drastically reduced the tissue oxygen tension is not as low in the area supplied If collateral circulation does not increase and the oxygen potential remains low more than 5 minutes the blood in the smallest branches of the veins is seen to be darker and thicker progressing to black and segmentation of static tightly packed red cells often in rouleau formation occurs This represents stasis in the part of the cortical capillary net underlying the small venule As ischemia becomes worse more venules and then larger veins draining a whole area become engorged with dark anoxic segmental masses of clumped cells After this stasis begins to appear in small arterioles entering the cortex White thrombi are not seen in this process If local blood flow improves the tissue oxygen potential ultimately may recover remarkably Increasing the blood pressure restores the neurologic potential Anticoagulation with heparin tends to retard this microstasis

The consistent appearance of segmentation and stasis in the terminal venules as the first event after occlusion of a large cerebral vessel appears to be an important clue to the pathogenesis of cerebral infarction Endothelial damage and stasis are important in producing massive infarction The formation of thrombi is not significant in the process of ischemia and anoxia produced by these methods Even when portions of thrombotic embolus lodge in a cortical vessel microstasis is manifest In many conditions called cerebral thrombosis the primary event is ischemic anoxia leading to patchy then confluent microstasis of the venous side of the capillary net

Normally hemoconcentration occurs on the venous side of the capillary circulation and is increased by a reduced rate of blood flow and increased permeability of the vessel walls The blood viscosity increases and the area is predisposed to stasis When the vessels are damaged due to the anoxia the process of infarction begins in the terminal venules The restoration of local blood flow via collaterals in

areas of vascular damage results in an increased capillary filtration rate and local brain edema

Infarction from anoxia is primarily due to damage to vascular endothelium with resulting edema hemoconcentration, sludging and stasis Anoxic anoxia has the same effect as ischemic anoxia The mechanism is common to all types of vascular insufficiency resulting from obstruction at a distance including embolism

**Localized Changes in Properties of Blood and Effects of Anticoagulant Drugs in Experimental Cerebral Infarction** Recent clinical reports stress benefits of anticoagulant therapy in thrombosis of the basilar and carotid arteries and in thromboembolic cerebrovascular disease John S Meyer[6] (Harvard Med School) with the technical assistance of Robert C Struzziero studied in detail the changes leading to circulatory standstill in the pial vessels during experimental infarction in 23 monkeys and 11 cats The collateral circulation was improved by use of heparin and Dicumarol® In normal cortex the blood flow within vessels was rapid and individual blood cells could not be identified An axial blood flow was present so that a thin line of clear plasma was observed next to the wall Arteries did not pulsate

Occlusion of the middle cerebral artery near the circle of Willis in cat and monkey regularly produced a series of changes visible in the pial vessels In the normotensive animal pial circulation immediately slowed pial artery anastomoses dilated and cortical oxygen tension decreased to 40 75% of normal readings The axial flow of cells became granular and white cells marginated to the edge of the stream where they tended to adhere momentarily to vessel walls impeding the flow of red cells In many capillaries plasma continued to flow but without cellular elements This stage persisted for 1 12 hours followed by increase in collateral blood flow after which reactive hyperemia was noted oxygen tension was higher than normal and diapedesis and small hemorrhages occasionally occurred around terminal venules

If while the animal was hypotensive there was occlusion of the middle cerebral artery and of a principal collateral vessel the collateral circulation failed to compensate The cortex immediately paled due to collapse of small vessels

(6) N w E g a J M d 258 151 159 J 23 1958

After 15 30 minutes the brain swelled visibly and oxygen tension was reduced to 5 20% of normal Red cells adhered to each other and formed large clumps in veins Hemo on centration was noted in terminal venules in the ischemic area Blood flow was progressively impeded until segments of red cells ceased moving and became static Several hours later groups of platelets agglutinated If collateral circulation failed for more than 48 hours arterioles and venules became static The resulting ischemic anoxia occasionally resulted in progressive brain swelling with visible compression of the cortex against the skull window and collapse of the pial vessels thus further compromising the cortical blood supply If collateral blood flow was resumed in 4 days stasis was commonly reversed

When heparin or Dicumarol® was given before vascular occlusion blood flow became slowed but to lesser degree Cortical oxygen tension was reduced to almost the same degree and cyanosis pallor and collapse of small vessels were observed Erythrocytes did not clump white cells did not adhere to the vessel walls platelets did not agglutinate and platelet thrombi did not form

Severe ischemic anoxia damages nervous tissue and vascular endothelium Cerebral infarction may occur in presence of continued circulation that is insufficient to meet the metabolic needs of the tissue for survival When cortical oxygen tension falls below 20% for more than 1 hour infarction regularly occurs Prolonged severe ischemia eventually results in necrosis of the smaller cerebral vessels Anoxia of the endothelium results in fluid loss from the blood the brain swells rapidly the vessel walls are permeable and plasma concentration increases All the formed elements become adhesive and blood viscosity increases apparently due to local change in the physical properties of the plasma Administering heparin and Dicumarol® prevents this localized change increase in local cerebrovascular resistance is prevented and better collateral circulation is promoted When ischemia is severe the anticoagulant drugs do not prevent cerebral infarction despite continued blood flow

► [This study would appear to furnish a rational experimental basis for the clinical results reported in the succeeding abstract The value of anticoagulant therapy in patients with cerebral embolism cerebral thrombosis and repeated brief attacks presumably due to temporary cerebral ischemia would now seem to be established beyond question —Ed ]

**Immediate Treatment of Cerebral Embolism** was inves tigated by A Barham Carter[7] in a controlled clinical trial in four groups of patients (1) a control series (2) patients treated by repeated stellate block (3) those treated by one stellate block and anticoagulants and (4) those treated with anticoagulants alone Diagnosis was based on the sudden appearance often within seconds of hemiplegia hemianop sia or aphasia in patients with atrial fibrillation subacute bacterial endocarditis recent myocardial infarction or mi tral stenosis without fibrillation Lumbar puncture was done in each case to exclude hemorrhage

With few exceptions most of the possible neurologic re covery from cerebral embolism takes place in the first 4 weeks and little change apart from that due to re education can be expected after 3 months Almost all patients surviving embolic hemiplegia regain some movement of the shoulder and lower limb

At the end of 3 months there was no significant difference between the controls and those treated by repeated stellate block There was no significant difference between those who received one stellate block followed with anticoagulants and those who received anticoagulants alone When all pa tients who had received anticoagulants were compared with those who had not there was a significant reduction in mor tality among the former and the number of recoveries was markedly increased The anticoagulants were heparin and phenylindanedione started immediately on admission

Anticoagulant therapy if properly given and supervised is without danger and is advantageous in treating cerebral embolism Stellate ganglion block has no effect on the final outcome

**Eye Symptoms in Intracranial Aneurysms and Angiomas** are described and discussed by Hans Wolfgang Zielinski[8] (Univ of Cologne) on the basis of a study of 245 cases (83 sacculated arterial aneurysms 21 traumatic arteriovenous aneurysms 124 arteriovenous angiomas and 17 cases of Sturge Weber disease)

Sturge Weber disease is the easiest to differentiate When the ophthalmologist is consulted because of glaucoma the full syndrome usually is apparent i e nevus flammeus of

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the face glaucoma and x ray calcification of the brain in the region of the venous intracranial angioma In all 17 cases there were calcification and facial nevi Epileptiform attacks are often present as confirmatory evidence When homonymous hemianopsia is present there is almost always a tumor like angioma deep to the choroid plexus arising in the posterior horn of the lateral ventricle

Diagnosis of traumatic arteriovenous aneurysms is also easy because of a history of injury (usually with fracture at the base of the skull) and subjective (verifiable by auscultation) intracranial vascular noises Pulsating exophthalmos is characteristic but nonpulsating exophthalmos does not exclude this condition When an intracranial vascular noise is noted unilateral optic atrophy with striking venous stasis and spontaneous venous pulsation is necessary to confirm the diagnosis (Trauma may be lacking since spontaneous arteriovenous aneurysms are possible ) Pulsating exophthalmos is pathognomonic of arteriovenous aneurysm (carotis cavernosus) only if other homolateral symptoms (noises motor and sensory disturbances) indicate a lesion of the sinus area It is found also with transmitted brain pulsation (x ray orbital defect) or intraorbital tumors (intracranial vascular noise lacking) but not with brain tumors Nonpulsating exophthalmos in arteriovenous aneurysms homolateral optic atrophy and motor disturbance may simulate a sphenoid meningioma Sudden onset of all symptoms usually with severe headache indicates an aneurysm In the cases studied unilateral papillary stasis genuine atrophy amaurosis motor disturbance protrusion sensory disturbance and increased tension furnished certain indication as to the side affected Bilateral pulsating exophthalmos occurs occasionally in unilateral aneurysm bilateral aneurysm is extremely rare Unilateral contralateral exophthalmos is also rare in such cases the vascular noise provides the differentiation

In arterial sacculated aneurysms diagnosis is more difficult especially when severe hemorrhage due to rupture is absent Often satisfactory diagnosis can be made only by angiography of the carotis In the presence of massive hemorrhage intracranial symptoms are so prominent that eye findings merely aid in localization Their recognition is much more important in paralytic cases Eye symptoms var

ying in degree and type over a long period (recurring visual impairment or squint) without other signs of an intracranial lesion are typical *Ophthalmoplegic migraine should also* suggest the possibility of aneurysm Striking retinal hemor rhages with slight papillary stasis are typical In basal tu mors bone is frequently destroyed this occurs but rarely in aneurysms Differential diagnosis of intrasellar aneurysm is particularly difficult since symptoms may mimic those of hypophysial tumor (optic atrophy bitemporal visual field loss widening of the sella endocrine symptoms) In this site angiography also often fails since these aneurysms tend to thrombose easily and then cannot be visualized Fine sickle shaped shadows in the sellar region may sometimes confirm the diagnosis In differential diagnosis of lesions near the sella sudden onset of eye symptoms (motor dis turbances amaurosis) with bitemporal hemianopsia and a normal sella (distinguished from intrasellar cases) favors a diagnosis of aneurysm rather than tumor However sudden impairment of vision may be caused also by hemorrhage in a cystic tumor (pituitary adenoma) In the cases studied unilateral atrophy amaurosis motor symptoms exophthal mos and sensory disturbances always occurred on the same *side as did homonymous hemianopsia Unilateral papillary* stasis however was also found contralateral to the aneu rysm With a paralytic course and total optic atrophy there is alway a very large usually broad based aneurysm un suitable for intracranial operation Homonymous hemianop sia and carotid aneurysm confirmed by angiography also indicate a poor prognosis because dorsal development of *the aneurysmal ac makes operation difficult*

Arteriovenous angiomas are the most difficult to differen tiate from brain tumors because in many cases symptoms are identical Tumor like angioma and large intracerebral hema tomas following rupture behave as space occupying lesions Differentiation of angioma depends on the history Late ap pearance of visual disturbances and pronounced papillary sta is are typical of cerebellar angioma The relation of ret inal bleeding to papillary stasis is the same as in arterial sacculated aneurysms (severe hemorrhages with slight pap illedema) Spasm headache and paresis with retinal angio matosis usually indicate angiomatous vascular anomaly in the brain

Differentiation from brain tumor with a paralytic course is extremely difficult on the basis of ophthalmologic symptoms alone In many cases diagnosis is made by angiography While unilateral papillary stasis and motor disturbances and homonymous hemianopsia are homolateral signs unilateral exophthalmos and more pronounced papilledema (when papillary stasis differs in the two eyes) may be contralateral in a third of the cases In the cases studied homonymous hemianopsia was always a sign that the angioma was connected with the middle cerebral artery Papillary stasis was found most often if the vascular anomaly lay in the region of the sylvian vascular group The very rare bitemporal hemianopsia in angioma was in a frontal location while homonymous upper quadrant hemianopsia always indicated occipital localization a homonymous lower quadrant hemianopsia always a deep lying angioma in the lateral ventricles the basal ganglions or the insular region

Severe papillary stasis with a long paralytic course signifies a tumor like angioma with large aberrant and efferent vessels offering an unfavorable surgical prognosis Conversely papillary stasis with a short apoplectiform course indicates an angioma well delimited from the brain by a hematoma with small exit and inflow vessels and good operability

**Surgical Treatment of Atherosclerotic Occlusion of Internal Carotid Artery** The syndrome of transient cerebral ischemia most often is due to segmental plaques in the innominate common carotid internal carotid or vertebral arteries in an extracranial segment Earlier attempts to treat occlusion of the internal carotid artery by procaine block cervical sympathectomy denervation of the contralateral carotid sinus thromboendarterectomy carotid jugular fistula and anticoagulants were unsuccessful Recently the occluded segments have been successfully replaced by grafts

Champ Lyons and Garber Galbraith[9] (Med College of Alabama) report their experiences in 6 patients During the procedure a shunt from the subclavian to the distally patent internal carotid maintained circulation to the brain and obviated the need for hypothermia The patients selected for this type of procedure should present no evidence of myocardial infarction or ECG changes Occlusion of the inter

(9) Ann Su g 146 487 496 S pt mber 1957

nal carotid artery must be demonstrable by carotid arteriogram This usually is found at or within 2 cm of its origin from the bifurcation

TECHNIC—An incision is made over the sternocleidomastoid muscle and the internal carotid artery is dissected free. If the arteriogram shows complete obstruction the artery is longitudinally incised If the distal portion is patent back bleeding will occur and the procedure can continue If no back bleeding occurs the artery is closed or ligated and the operation concluded If the artery is distally open a separate incision is made over the subclavian artery and end to side anastomosis is made between it and a crimped nylon prosthesis which then is passed through a tunnel under the sternocleidomastoid and sutured end to side into the internal carotid

The shunts were successful in 5 patients and 4 survived without significant neurologic signs or symptoms

No method of palpating the pulses in the neck suffices to identify internal carotid occlusion A bruit is audible only when the occlusion is incomplete Adequate early diagnosis depends on more frequent use of carotid arteriography in patients with the little stroke syndrome Carotid bypass should be considered for the patient with cerebral claudication before major infarction occurs

**Intracranial Internal Carotid Artery Aneurysms Results of Treatment by Cervical Carotid Artery Ligation** H A Shenkin P Polakoff and B E Finneson[1] (Philadelphia) followed for an average of 3 2 years 19 consecutive patients treated by cervical carotid artery ligation Age range was 24 70 with average age of 47 5 at time of operation Results are presented in support of previous reports that this treatment is adequate for intracranial aneurysms of the internal carotid artery has the lowest accompanying morbidity and mortality and protects against recurrent hemorrhage

Eighteen patients were hospitalized for subarachnoid hemorrhage 5 of these had hemorrhage previously One patient presented with headache and 3d nerve palsy of 3 months duration On admission 3 patients were semicomatose and 4 were mentally obtunded All except 1 who died postoperatively were fully conscious at time of ligation The patient who died a man 59 was semicomatose with subarachnoid hemorrhage from an aneurysm of the left internal carotid artery located between the origin of the posterior communicating vessel and the bifurcation he had hemorrhage into the left frontal lobe In 8 patients the aneurysms were lo

(1) J Neu g 15 183 191 M h 19 8

cated at or near the origin of the posterior communicating artery in 5 at the bifurcation of the internal carotid and in 5 between these two sites Bilateral arteriography generally was delayed until the patient was conscious and stabilized Average length of time from onset of hemorrhage to carotid vessel ligation was 14 days The 18 patients survived 6 months to 7 5 years without secondary hemorrhage 17 are well and economically useful and 1 is permanently incapacitated with hemiplegia

When patients are relatively stabilized and conscious cervical ligation can be carried out safely Definitive surgery should be deferred if the patient is unconscious Surgery does not remedy the neurologic deficit caused by severe subarachnoid hemorrhage Of necessity surgery adds to the deficit that cerebral circulation has to overcome The primary objective is prevention of recurrent hemorrhage which is best attained when the neurologic deficit is at a minimum Any intracranial approach increases the likelihood of mortality and morbidity

Although cervical ligation of the carotid artery is effective and relatively safe in treating intracranial aneurysms of the internal carotid artery the procedure is singularly dangerous when the aneurysm is located on the anterior cerebral or anterior communicating artery

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## PERIPHERAL CIRCULATION

**Portacaval and Portapulmonary Anastomoses in Laennec s Cirrhosis and in Heart Failure** Arterial blood oxygen is decreased in patients who have cirrhosis of the liver but no defect of alveolar capillary diffusion has been detectable Anastomoses between the portal venous system and the superior caval system are prominent in such patients and anastomoses between the pulmonary bronchial and azygos veins are also present These in the presence of portal hypertension might lead to admixture of unsaturated portal venous blood to oxygenated pulmonary venous blood Paul Calabresi and Walter H Abelmann (Harvard Med School) injected a radiopaque lead gelatin mass into the portal vein in situ

( ) J Clin Invest 36 1 57 1 65 A gust, 1957

of cadavers of 10 patients who had cirrhosis of the liver 6 with heart failure and 4 with no evidence of functionally significant hepatic or cardiac disease

In all cases of cirrhosis thoracic portacaval anastomoses were prominent The short gastric and coronary veins anastomosed with both the submucosal esophageal and periesophageal venous plexuses The submucosal esophageal veins were generally varicose The periesophageal plexus was consistently dilated and anastomosed freely with the mediastinal pleuropericardial and azygos veins In 4 patients the mediastinal venous plexus anastomosed with the bronchial veins and in 2 the injected material was present in the pulmonary veins and in the left atrium Thus both portacaval and portapulmonary anastomoses may exist in cirrhosis with portal hypertension

Similar venous pathways were demonstrated in 6 cases of heart failure and in 4 patients who had neither heart failure nor cirrhosis In these the anastomoses were less prominent and the pulmonary veins did not fill with the injected mass

These studies demonstrated that besides the recognized portacaval anastomoses portapulmonary anastomoses may exist When the pressure gradient between the portal and pulmonary veins becomes significant these anastomoses may act as portapulmonary shunts, bypassing the lungs and reducing the oxygen saturation of the arterial blood

**Treatment of Intermittent Claudication Preliminary Report** Intermittent claudication is the most difficult to treat in peripheral vascular disease All agents directed toward improving the blood supply to the lower extremities have been ineffectual in relieving this symptom Some success has been achieved with adrenergic blocking drugs but results have not been uniform or reliable Graft replacement of blocked arterial segments has been notoriously ineffective and in many patients has increased the symptoms Tranquilizing drugs reportedly have relieved various painful disorders of skeletal muscle spasm

Saul S Samuels[3] (New York) treated 20 patients for 3 months with a new tranquilizer phenaglycodol (Ultran) All had severe intermittent claudication associated with arteriosclerosis obliterans Dosage was 300 mg 3 times daily by mouth In all walking ability promptly improved re

(3) A g I gy 8 01 Ap 1 1957

markably with distinct relief of painful and disabling symptoms The drug was amazingly efficient in relieving intermittent claudication

► [Walking several times a day to the point of minimal symptoms is one of the most effective methods of treating intermittent claudication Anticoagulants are likewise very valuable in some patients —Ed ]

Medical Management of Peripheral Ischemic Diseases is reviewed by Edgar A Hines Jr and Ray W Gifford Jr[4] (Mayo Clinic and Found ) Spasm of unoccluded arteries is common when a major vessel to an extremity is suddenly occluded This is a major contributing factor to the immediate severe ischemia of the limb and may endure for minutes or even hours severely damaging the endothelium distal to the occlusion The arterial spasm must be quickly relieved and measures promptly instituted to prevent further thrombosis

Diagnosis must be made rapidly and proper treatment started immediately The extremity must not be elevated nor heat applied in any form The Sanders oscillating bed should be used in the maximal low foot and minimal low head position when this is not available the head of the bed should be elevated 12 15 in Room temperature should be maintained at 80 90 F Papaverine hydrochloride ½ gr or Priscoline® 25 50 mg, should be given intravenously or preferably intra arterially proximal to the occlusion Whisky should be given 1½ oz every 4 hours Sympathetic block may be beneficial if done immediately Anticoagulation should be started preferably using heparin and a coumarin derivative Local trauma must be avoided When medical treatment is started within 12 hours of onset but circulation does not improve within the next 2-4 hours embolectomy or thrombectomy may be attempted

In chronic occlusive arterial disease surgery is effective only when the occlusive disease is limited to segments of the larger arteries Even in these circumstances occlusive disease may subsequently develop at other sites Since many patients are in the older age groups and have coronary or cerebral arterial disease as well the hazards of major surgery are high

Tobacco is potentially harmful to all who have occlusive arterial disease because it constricts small arteries and arterioles thereby compromising collateral circulation Ab

(4) Am. J Med. 23 724 729 N mbe 1957

stinence is helpful in treating all types of occlusive arterial disease but is essential in treating thromboangiitis obliterans

Atherosclerosis undoubtedly is related to lipid metabolism Lipemia which often is associated with arteriosclerosis obliterans sometimes can be controlled by limiting dietary fat intake to 30-40 Gm daily Lipotropic agents thyroid extract and sitosterols have not produced consistent results The feminizing effects of estrogens and the inconvenience and expense of heparin administration have prevented wide acceptance of these

Once major arteries are occluded they remain so despite any medical treatment available Medical treatment is intended to take maximal advantage of collateral circulation by eliminating arteriospasm and promoting dilatation of collateral channels Many drugs are advertised and advocated for use in dilating the peripheral arteries including Priscoline® nicotinic acid Dibenzyline® hexamethonium Ilidar® and Arlidin® Most of these are effective vasodilators for normal persons and in certain vasospastic conditions *but are disappointingly ineffective in extensive organic occlusive* arterial disease Whisky 1 2 oz before meals and at bedtime is as good as and perhaps superior to any peripheral vasodilating drug available Postural or Buerger s exercises have been advocated but are of little value and are unwarranted for routine use The Sanders oscillating bed affords postural exercises to the entire body with no effort by the patient Hospitalized patients may be placed on this bed for 8 24 hours Other mechanical devices such as the alternating positive and negative pressure boot and an apparatus to produce intermittent venous occlusion have been abandoned Fever therapy if used should be reserved for patients with ischemic lesions due to thromboangiitis obliterans because they are younger and better able to tolerate it A warm environmental temperature promotes vasodilatation and can be obtained by a controlled heating unit the temperature must never exceed 90 F the heat must never be applied directly

Regional sympathetic denervation often is helpful in increasing arterial circulation to the skin of ischemic extremities and is indicated when ischemia of the skin is extensive

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and its integrity is jeopardized It may promote healing of ischemic ulcers and help prevent their recurrence

Medical treatment of intermittent claudication is not satisfactory Heparin testosterone and all the vasodilating drugs are worthless Occasionally a course of deproteinated pancreatic extract, 5 cc daily for a week every other day for 2 weeks then twice weekly may be helpful Usually patients can be taught to live with intermittent claudication They should be assured that it will do no harm to walk to tolerance as desired and it probably is beneficial to do so Since ischemia of the skin not the muscle leads to irreversible gangrene and amputation patients must be taught to be more concerned about proper care and hygiene of the feet than about the distance they can walk

The patient must be ever vigilant to avoid crushing or bruising ischemic hands or feet scratches cuts fissures in the skin and burns blisters and frostbite Only comfortable shoes that do not bind or rub should be worn new shoes should be broken in gradually The feet must not be immersed in hot water and hot water bottles or heating pads must not be applied directly to the feet Toenails should be cut straight across Corns calluses and bunions should not be trimmed or incised If the skin is excessively dry and tends to crack or scale hydrous lanolin or cocoa butter should be applied gently every day Patent medicines for treating corns calluses and athlete s foot should be avoided Adhesive tape or plaster should not be applied to the skin of ischemic extremities

In treating ischemic ulcers conservatism is the wisest course Ointments impede healing The risk of sensitivity precludes use of local antibiotics If sensitive organisms are cultured the appropriate antibiotic may be given systemically When a necrotic crust or eschar covers the ulcer enzymatic debridement using wet dressings of streptokinase and streptodornase may help in removing the crust Surgical debridement should be avoided but if necessary should be gentle and conservative After infection subsides application of dry powdered blood cells to the ulcer often promotes healing

**Aneurysms of Abdominal Aorta** in most cases are due to arteriosclerosis and with the advancing age of the population their incidence is increasing Resection of the aneu

rysm and insertion of a graft is the most successful therapy F Henry Ellis Jr John W Kirklin and Philip E Bernatz[5] (Mayo Clinic) summarize results in 133 patients

If such aneurysms are untreated the prognosis is poor About 80% of patients die within 5 years of the time diag nosis is first established Death is most commonly due to rupture of the aneurysm The presence of an abdominal aor tic aneurysm is a constant threat and the time of a cata strophic rupture cannot be predicted A large aneurysm and the presence of symptoms are poor prognostic signs but small asymptomatic aneurysms can also rupture fatally

*In most cases* diagnosis is made by palpation of a large pulsating mass in midabdomen at or above the umbilicus and extending to the left Pain is frequent often vague but may be severe and penetrate to the back and does not nec essarily indicate leakage An anteroposterior roentgenogram may demonstrate a rim of calcium pathognomonic of aneu rysm

*All patients under age 70 with no associated serious disease* should be urged to have surgery even if the aneurysm causes no symptoms If they have severe coronary artery disease and the operative risk is extremely high surgery is prob ably contraindicated Those with milder atherosclerotic dis ease should have surgery Evidence of leakage is an urgent indication for operation The risk is high but the outcome *is fatal if the condition is uncorrected The age of the patient* alone is no contraindication

In most patients preoperative evaluation cannot establish whether or not important vessels are involved In the vast majority abdominal aortic aneurysms arise below the renal arteries and a cuff of relatively normal aorta is available to which the graft can be sutured Of the total 133 patients 10 (7 5%) were found to be inoperable at exploration because th renal arteries were involved The other patients had resection and grafts The over all mortality rate was 15 4% Elective operations in which an aortic homograft was used had a mortality rate of *12 6%*

The procedure is straightforward An aortic homograft has been preferred removed from suitable donors aged 10 50 within 4 hours of death and stored at 2 4 C The freeze dry technic may be more advantageous Suture of all anas

(5) S Cl N rth Am 37 1047 1057 A g t 1957

tomoses is with 5 0 silk Total aortic occlusion time should rarely exceed 60 minutes

**Aneurysms of Abdominal Aorta and Its Branches Study of Untreated Patients** Marvin L Gliedman William B Ayers and Betty L Vestal[6] reviewed autopsy records of Kings County Hospital Brooklyn for 1940 55 and found 68 patients (52 men 16 women) aged 29 93 with mean age of 70 who had had 96 abdominal aneurysms The natural history of untreated aneurysms was derived from this group Arteriosclerosis syphilis and mycotic emboli were the 3 main causes accounting for 49 14 and 3 cases respectively Two patients had abdominal coarctations below the renal arteries with severe arteriosclerosis and aneurysms below the coarctations Of the 96 aneurysms 72 were aortic 18 iliac 3 splenic 2 hypogastric and 1 superior mesenteric Symptoms varied from none in 19% to vague abdominal complaints in some and excruciating back pain in others Similarity to primary genitourinary disease led to admission to urology service in many instances

Nearly half the patients died of rupture Almost another third died of disease considered directly related to the cause of the aneurysm severe coronary cerebral or renal arteriosclerosis or heart failure due to syphilis An additional one fifth had disease related to the aneurysm listed as a primary or major cause of death Thus 96% of those who died with abdominal aneurysms died of rupture or a disease directly related to the cause of the aneurysm

Of the 68 patients 35% showed definite evidence of an old or recent myocardial infarction Hypertension was present in 24 of the 51 patients whose aneurysm was due to arteriosclerosis Vascular rupture might have been forestalled in 48% by grafting but the question of whether ultimate survival would have been longer remains unresolved Incidence of 35% myocardial infarction in the patients of advanced age is not conducive to long survival

These patients pass through three phases asymptomatic symptomatic prelude and rupture Survival depends on the phase the patient is in at the time of diagnosis Patients with symptomatic aneurysms should be treated immediately Those without symptoms should be selected for surgery on the basis of risk

(6) \ S g 146 207 14 \ g t 1957

**Alterations in Renal Hemodynamics during Controlled Extracorporeal Circulation in Surgical Treatment of Aortic Aneurysm** are described by George C Morris Jr Raymond R Witt Denton A Cooley John H Moyer and Michael E De Bakey[7] (Baylor Univ ) A temporary vascular shunt is effective in preventing renal and spinal cord damage during occlusion of the aorta Side branches can be attached to the carotid arteries to maintain cerebral circulation For aortic bypass to facilitate resection of aneurysms arising in the descending thoracic aorta a proximal catheter was placed in the left atrium or left subclavian artery and a distal catheter in one common femoral artery for return of blood When cardiopulmonary bypass was needed during resection of aneurysms of the aortic arch a pump oxygenator was used removing venous blood from the venae cavae pumped through a modified DeWall Lillehei oxygenator and returned through a femoral catheter Renal blood flow and glomerular filtration rate were measured as estimates of the effectiveness of the perfusion blood flow

Renal blood flow and glomerular filtration rates in patients who had the aortic bypass generally correlated well *with the blood pressure Anesthesia and thoracotomy had* little effect on average renal blood flow During bypass with the pump renal blood flow fell to a mean of 10% of control levels and glomerular filtration to 7% of control levels In 2 patients with the lowest pressures in the lower aorta 28 mm *Hg renal function* was not measurable *Immediately after* release of the occluding clamps renal blood flow generally returned toward normal but glomerular filtration remained somewhat depressed

In patients with cardiopulmonary bypass there was no *proximal distal pressure differential* because the entire body was perfused The mean aortic pressure averaged 44 mm Hg and measurable renal function generally was greater than in patients with the aortic pump bypass Renal blood flow averaged 24% of control and glomerular filtration rate 29% After resumption of normal circulation the renal blood flow and glomerular filtration rate returned to 72% and 80% of control values respectively

These studies indicate that pump-flow rate of 20 cc /kg body weight is necessary to support a lower aortic pressure

(7) J Th S g 34 590 598 N mbe 1957

that is sufficient to allow renal function when the aortic by pass pump is used In controlled extracorporeal circulation with a pump oxygenator perfusion of 35 cc/kg supports renal function

**Current Concepts on Management of Shock** The term shock denotes protracted prostration and hypotension usually accompanied by pallor coldness and moistness of the skin collapse of superficial veins altered mental status and suppression of urine formation Rational and effective treatment requires diagnosis of the specific cause Max H Weil[8] (Mayo Clinic) classifies the causes of shock into 6 groups hypovolemia cardiac failure bacteremia hyper sensitivity neurogenic factors and obstruction to blood flow

Intravenous injection of endotoxins from Brucella meli tensis or Escherichia coli is followed within 1 minute by a sharp fall in arterial pressure and increase in portal venous pressure Large amounts of blood pool in the liver and in testines and the volume of blood returning to the heart is correspondingly decreased In time coronary flow may be sufficiently decreased to cause defective myocardial con tractility and thus further decline in cardiac output and arterial pressure Hypovolemia results from hemorrhage dehydration loss of protein or capillary leakage When a third of the total blood fluid is lost a critical point is reached at which the volume of blood is no longer sufficient to fill the vascular bed Venous return and cardiac output are so low that compensatory vasoconstriction is insufficient to maintain the arterial pressure Cardiac failure reduces car diac output sometimes severely enough to produce shock

Hypersensitivity and anaphylactic reactions cause shock probably by sudden constriction of small hepatic veins re sulting in pooling of blood in the portal venous bed and sud den reduction in venous return and cardiac output Thus the initial hemodynamic disturbance is similar to that of shock associated with bacteremia In absence of normal vasocon strictive impulses after transection of the spinal cord sym pathectomy administration of certain anesthetic agents or drug induced ganglionic blockade normal neurogenic con trol of vessel caliber is lost The venous bed increases so that the volume of blood is inadequate to fill it and venous re turn and cardiac output are reduced Loss of venomotor tone

(8) Circulation 16 1097 1105 December 1957

rather than decreased arteriolar resistance is the major defect in this type of shock Physical obstruction of a main vessel reduces total blood flow to the point that it is inadequate to maintain circulation venous return and cardiac output Examples are pulmonary embolism and dissecting aneurysm

Vasopressors are valuable in treating shock The most potent are norepinephrine or levarterenol (Levophed®) and metaraminol (Aramine®) Less potent drugs such as methoxamine (Vasoxyl®) phenylephrine (Neo Synephrine®) and mephentermine (Wyamine®) may be effective in transient hypotension

Levarterenol and metaraminol are useful in treatment of shock due to myocardial infarction bacteremia or hypersensitivity reactions and are usually favorable in neurogenic shock The benefit is only partly due to improved coronary blood flow which follows elevation of systemic blood pressure Both drugs directly increase contractility of myocardial fibers In bacteremic anaphylactic shock obstruction to outflow is reduced in the splanchnic veins and the pooling is remedied Epinephrine is the drug of choice for immediate treatment of acute anaphylactic shock Use of vasopressors is seldom justified in hypovolemia Blood plasma and electrolyte fluids or plasma expanders in an emergency are indicated If shock persists after replacement of fluids vasopressors may be helpful In the shock of physical impediment drugs that produce additional vasoconstriction are not ordinarily indicated

Levarterenol may injure tissues at the injection site but local infiltration of adrenergic blocking agents such as tolazoline hydrochloride (Priscoline®) or phentolamine hydrochloride (Regitine®) is effective treatment for this complication The effect of levarterenol is transient and constant supervision is required Metaraminol causes no local injury may be injected intravenously intramuscularly or subcutaneously without additional fluid vehicle and has prolonged action It reportedly produces less renal vessel constriction than does levarterenol for a dose that produces comparable pressor effects After intravenous administration its effect is noted in 1 2 minutes is maximal in 5 and persists for 20 25 minutes After subcutaneous injection its

effect is noted in 5 12 minutes is maximal in 30 and persists for 90 minutes

A patient in profound shock may first be given 3 10 mg metaraminol—directly into the femoral vein if necessary—which promptly elevates the arterial pressure and distends the peripheral veins permitting a normal intravenous infusion without requiring a cut down In most patients the pressure is well maintained by subcutaneous injections of 3 25 mg every 30 120 minutes Continuous intravenous infusion may be given in doses up to 500 mg/L With improvement the pressor response to metaraminol becomes more intense and the dose is reduced In presence of acidosis response to vasopressor agents is greatly diminished Molar sodium lactate re established responsiveness in the few patients in whom it was tried Further trial seems indicated

Adrenocortical hormones may be of striking benefit in shock due to bacteremia or hypersensitivity when life is threatened and may augment the effectiveness of vasopressors Hydrocortisone sodium succinate (Solu Cortef) is given in an initial intravenous injection of 50 100 mg and then maintained as a continuous infusion of 5 12 mg/hour Risk is small if the treatment period is short Indications for use of digitalis are the same whether or not shock is present Routine use for shock is of no proved benefit and may be injurious Chlorpromazine is of no proved value Hypothermia may be of some value The head down position provides only transient benefit and prolonged or routine use may delay recovery

**Host Resistance in Hemorrhagic Shock IX Demonstration of Circulating Lethal Toxin in Hemorrhagic Shock** is reported by Fritz B Schweinburg Paul B Shapiro Edward D Frank and Jacob Fine[9] (Boston) Hemorrhagic shock causes severe damage to the antibacterial defense mechanisms of the host animal Cultures from blood and tissues are consistently negative Yet if the shock is allowed to persist the peripheral vessels become refractory to transfusion

Dogs and rabbits were put into hemorrhagic shock and allowed to remain so until the shock became irreversible to transfusion They then were exsanguinated The blood or

(9) P oc Soc E per B l & M d 95 646-650 A g Sept. 1957

plasma was shown to be sterile by culture and then transfused into a healthy recipient animal Additional experiments were performed with donor blood from dogs that had been given nonabsorbable antibiotics orally and by rectum before shock was induced

The results showed a lethal substance in the blood of dogs and rabbits in advanced hemorrhagic shock This was not a bacteria but a toxin that the animal in shock apparently cannot detoxify Source of the toxin appears to be intestinal bacteria The toxin is present in the blood liver lymph lung and spleen Normal dogs tolerated infusion of blood from dogs dying of advanced hemorrhagic shock without noticeable harm Dogs in hemorrhagic shock recovered rapidly and without signs of illness when transfused after 2 hours with normal donor blood or with their own shed blood But about 70% of such dogs died when the transfused blood was from dogs dying of prolonged hemorrhagic shock After the transfusion most of the recipients were unable to stand drink or take fluid and showed bloody diarrhea until recovery or death However when the donor was vigorously pretreated with nonabsorbable antibiotics only 37% of the recipients died and the survivors recovered rapidly without signs of illness

The greater tolerance to prolonged shock in animals pretreated with nonabsorbable antibiotics appears to be due to elimination of bacterial endotoxins by the antibiotics The hemorrhagic lesion in the gut of shocked animals is produced by the toxin and not by the shock itself A toxin with the same properties as the toxin present in the blood of hemorrhagic shock apparently also is present in the blood of animals in other types of shock

**Complications of Aortography** were observed in 6 patients by James E Anthony Jr[1] (Presbyterian St Luke s Hosp Chicago) in a total of 100 aortograms This is higher incidence than was expected from various reports in the literature Most frequent but fortunately not serious was pain in the back abdomen or extremities Paraplegia developed in 1 patient probably representing spinal cord damage secondary to retarded blood flow in the abdominal aorta lowered blood pressure incidental to the procedure and compression of the aorta by position Perirenal abscess devel

(1) A M A A h S g 76 8 34 J ) 1958

oped in 1 patient retroperitoneal hemorrhage in 1 hemothorax in 1 chemical pyelonephritis in 2 and extravasation of dye with severe pain in 1

Translumbar aortography is valuable in diagnosis as an adjunct to simpler safer more revealing studies The hazards however must be carefully weighed against the benefits from the probable information to be received The procedure is indicated in complete ureteral obstruction when intravenous pyelography shows nothing and catheterization is impossible when preoperative appraisal is necessary to determine whether the kidney may be partially salvaged when renal cysts must be differentiated from tumors for demonstration of aberrant vessels and in Leriche s syndrome or when there is evidence of unilateral or bilateral iliac artery occlusion

Contraindications include acute coronary occlusion or cerebrovascular accident impaired renal function skeletal deformity allergy to dye cachexia poor hepatic reserve bleeding advanced tuberculosis hyperthyroidism and when the information to be obtained does not justify the risk

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## HYPERTENSION

**Clinical Course and Pathology of Hypertension with Papilledema (Malignant Hypertension)** P Kincaid Smith J McMichael and E A Murphy[2] (Postgrad Med School London) reviewed case records of 197 patients (109 male 88 female) with malignant hypertension seen between 1935 and 1955 Pathologic material was available on 124 Malignant hypertension is a relatively rare complication affecting only 1% of persons who have systolic pressure over 170 mm Hg Incidence in young patients with hypertension is much higher Malignant hypertension seldom was noted after age 65 and nearly all the patients under age 30 had nephritis or pyelonephritis

As far as can be determined malignant hypertension complicates an antecedent benign hypertension Occasional cases have been recorded in which the malignant hyperten

(2) Q art J M d. 27 117 153 J y 1958

sion was considered to develop as a primary disorder but this was difficult to establish When the patients were carefully followed at least one reading of hypertension had been noted previously There is no malignant range of blood pressure reading and diagnosis cannot be made by these readings Wide swings in blood pressure occur spontaneously The cardinal diagnostic point is papilledema which rarely clears spontaneously Spontaneous clearing was noted in only 3 of the 197 patients Cerebrospinal fluid pressures were high on the average but many were within the normal range

Headache has been considered recently as a neurotic or anxiety symptom that develops in patients who are aware they are hypertensive but this was not confirmed in the present series Headache developed at any time during the hypertensive di ease sometimes years after its recognition but became increasingly severe and frequent as the malignant phase approached Dizziness was common and was the presenting symptom in a few Vision was impaired in 114 of 180 patients in whom it was documented Albuminuria was noted in 195 of the 197 patients

*Neurologic manifestations occurred in 79 of 190 patients* Of 65 such patients in whom cause of death wa ascertained 33 had a fatal neurologic incident (23 cerebral hemorrhage) Lower motor neuron facial palsy was present in 7 patients *Angina rarely was present Dissecting aneurysm was found* in only 1 of the 89 patients who came to autopsy before advent of methonium treatment

Of 105 untreated patients 55% were dead 2 months after diagnosis *and 90% within a year Only 1 survived 5 years* and still is alive 22 years after spontaneous disappearance of the papilledema Sympathectomy and removal of a unilateral diseased kidney in 24 patients altered prognosis only slightly reducing the mortality rate in 119 patients (including 105 untreated) to 82% at 1 year 3 patients survived to 5 years

The specific arterial lesions are the criteria for pathologic diagnosis of malignant nephrosclerosis The interlobular arteries show cellular hyperplasia of the intima which is even more specific than the accompanying fibrinoid degeneration in afferent arterioles Fibrinoid necrosis may occur in benign hypertension also The vascular and parenchymal le

sions of malignant nephrosclerosis represent the final stage of malignant hypertension

The mechanical effect of extreme elevation of arterial pressure alone is insufficient to explain the arteriolar necrosis Scattered arteriolar necrotic changes occasionally are noted in benign hypertensive kidneys Such changes can be intense in vessels distal to narrowed interlobular arteries If narrowing reduces pressure in the vessels beyond high pressure hardly could be responsible for arteriolar necrosis The tissue response could be the same if the vessels were damaged by some toxic influence or even allergy The characteristic vascular changes proliferative endarteritis and arteriolar necrosis were most extensive in the essential hypertensive group aged 30 60 The changes were less severe in the younger group with primary renal disease In patients over age 60 the changes were similar to those of benign hypertension

**Antihypertensive Drug Therapy in Management of Toxemia of Pregnancy** is reviewed by Alfred M Sellers[3] (Univ of Pennsylvania) The relation between essential hypertension and toxemic hypertension is obscure Women with essential hypertension tend to get toxemia more easily than those with normal blood pressure and the course of their cardiovascular disease thereafter may be accelerated Signs of toxemia most frequently develop in the 8th or 9th month of pregnancy in the group with true toxemia but may develop in the 4th or 5th month in those with hypertension and superimposed toxemia

The retinal fundi in toxemia are usually normal except for occasional segmental vasospasm In acute eclampsia hemorrhages and exudates may be present The incidence of hypertension and permanent vascular damage after toxemia is related more to the duration of the toxemia than to its severity

Patients discovered to have toxemia of pregnancy or hypertension associated with pregnancy should be admitted to hospital for complete studies including urinalysis quantitative urinary protein blood urea nitrogen uric acid intravenous phenolsulfonphthalein excretion test funduscopy ECG s orthodiagraphy daily blood pressure determinations and urinary output and body weight measurements

(3) A J M S 233 09 717 J 1957

Many patients with toxemia respond to bed rest sedation sodium restriction to less than 1 Gm /day and avoidance of excessive weight gain Strict fluid restriction is unnecessary if daily output is replaced and about 600 ml /day added to replace insensible loss

Before specific antihypertensive drugs were available treatment consisted of massive sedation and magnesium sulfate Sedation introduces the danger of marked respiratory depression of mother and fetus Magnesium depresses the central nervous system particularly the medullary centers and the danger of respiratory depression is great A solution of 10% calcium gluconate should be available as an antidote

The hypertension of toxemia responds poorly to ganglionic and adrenergic blocking drugs The combination of Apresoline® and reserpine constitutes potent therapy A a single agent parenteral reserpine is probably the agent of choice for managing toxemia of late pregnancy Mild hypertension uncomplicated by toxemia can be treated by a dose of 0 25 mg twice daily more severe hypertension can be treated by a priming dose of 1 mg 4 times a day and decreasing the dose over the next week to 0 25 mg twice daily In severe toxemia 2 5 mg reserpine intravenously or intramuscularly repeated every 8 12 hours is effective

The only known cure for toxemia is delivery of the fetus and this represents optimum therapy The current role of antihypertensive drugs is in allowing safe prolongation of gestation to the point of fetal viability Regardless of the blood pressure response to the antihypertensive drug delivery still must be performed at the moment most likely to assure fetal survival and least likely to injure the mother In severe eclampsia pregnancy should be terminated as soon as the blood pressure can be stabilized and pulmonary edema and convulsions controlled

**Treatment of Essential Hypertension with Chlorothiazide (Diuril®) Its Use Alone and Combined with Other Antihypertensive Agents** is described by Edward D Freis Annemarie Wanko Ilse M Wilson and Alvin E Parrish[4] (Georgetown Univ ) Pharmacologic studies in animals and man have shown marked increase in urinary excretion of sodium potassium and chloride after oral administration of

(4) J.A.M A 166 137 140 J 11 1957

chlorothiazide Ten patients previously untreated were hospitalized placed on a diet containing 1 25 Gm salt daily and an additional 3 Gm sodium chloride in tablets After the blood pressure had stabilized they were given orally 0 5 Gm chlorothiazide 3 times daily for 6 days The blood pressure fell in each patient the systolic an average of 18 7% the diastolic an average of 13 9% When chlorothiazide was withdrawn in 5 patients pressure gradually returned to pretreatment levels

Chlorothiazide 0 5 Gm twice daily was added to the regimen of 73 patients with hypertension 33 were being treated with ganglionic blocking agents with or without reserpine and/or hydralazine 19 were receiving veratrum alkaloids with or without other medication and 21 were taking reserpine alone or combined with hydralazine In each patient the blood pressure fell further In 32 of the 73 patients all other antihypertensive medications except chlorothiazide were withdrawn and the patients were maintained on chlorothiazide alone In 10 of the 32 patients blood pressure level over 1½ months did not rise but in 22 the level rose 10% or more in the diastolic In 6 of the 22 patients the elevation approached pretreatment or control levels Five patients who had lumbodorsal splanchnicectomy 6 months to 3 years earlier responded to chlorothiazide alone with significant additional reductions of blood pressure averaging —21% Fifteen hospitalized normotensive patients under the same controlled salt intake regimen showed no change in blood pressure when chlorothiazide was given No other antihypertensive agent has shown such specificity for hypertension

Most patients noted diuresis the first 1 2 days on chlorothiazide treatment Six complained of nausea and 4 of weakness during the 1st month of treatment but stopping the drug for 1 day promptly cleared these symptoms Chlorothiazide tended to exaggerate postural hypotension when it was present but did not produce it To prevent postural collapse the dose of ganglionic blocking agents had to be reduced when chlorothiazide was begun No sign of electrolyte depletion was observed but injudicious elevation of doses or continued administration of the drug with diets severely restricted in sodium or when significant extrarenal salt loss occurs might lead to severe electrolyte balance

**New Drugs for Hypertension with Special Reference to Chlorothiazide** are discussed by Robert W Wilkins (Boston Univ ) There is a difference in the so called emetic hypotensive ratio of the pure veratrum alkaloids (protoveratrine A and protoveratrine B) but for clinical purposes it can be said that the hypotensive dose of all available veratrum preparations is uncomfortably close to the nauseating dose Clinically there are no important differences among the various well standardized preparations of veratrum whether they are extracts alkaloidal mixtures or pure substances The starting doses of the commonly used preparations are Veriloid® 2 mg Vergitryl® 1 unit Provell® 0 25 mg Veralba® 0 25 mg and Protalba 0 1 mg given at least 4 hours apart 3 or 4 times a day These doses should be increased gradually until either the desired hypotension or nausea is produced

Standardized preparations of the crude root of Rauwolfia serpentina or alkaloidal extracts of this root are as useful clinically in hypertension as the pure alkaloids or their analogues Of the pure alkaloids reserpine is the most effective Daily oral doses of reserpine over 1 mg are not more effective for chronic antihypertensive treatment than doses up to 1 mg although increasing the dose up to 1 mg a day may increase the hypotensive effect of this drug Two or three months of continuous treatment may be necessary in certain patients to arrive at the full hypotensive effect of 1 mg reserpine orally a day after this time the dose usually should be decreased to prevent mental depression without loss of the hypotensive effect The suggested starting doses for rauwolfia preparations are Raudixin® 50 mg Rauwiloid® 2 mg and reserpine rescinnamine or deserpidine 0 1 mg 1-4 times a day These may be increased gradually to 100 mg 4 mg or 0 25 mg respectively 4 or 5 times a day However after 1 3 months dosages should be reduced to the minimal effective hypotensive dose to prevent mental depression nightmares or insomnia

Hydralazine remains the sole clinically useful representative of the direct renal vasodilators If used with rauwolfia or reserpine and in low gradually increasing doses hydralazine is usually well tolerated It is also frequently used in combination with various ganglion blocking agents The

(5) New Engl J Med 257 10 6-1030 N 1 1957

starting dose of hydralazine (Apresoline®) is 10 mg 4 times a day increased gradually as necessary to 50 or 100 mg 4 times a day On this regimen the late lupus like hydralazine syndrome has rarely been encountered

The various ganglion blocking agents cause troublesome effects in many patients such as faulty accommodation of the eye dry mouth and throat sluggish intestinal motility incomplete emptying of the bladder sexual impotence and particularly orthostatic arterial hypotension Wilkins suggests reserving these drugs for the most urgent and resistant phases of malignant hypertension Starting doses are hexamethonium (Bistrium®) 62 5 mg pentolinium (Ansolysen®) 20 mg chlorisondamine (Ecolid®) 10 mg and mecamylamine (Inversine®) 2 5 mg 2-4 times a day The individual successive doses of each drug should be carefully increased by no more than the amount of the initial dose until the desired effect on blood pressure (taken in the upright position) is obtained Since blood pressure is more responsive to blocking agents after sleep the first dose on awakening usually should be smaller than subsequent doses

It has been observed that reserpine markedly depletes the body of its natural stores of serotonin Furthermore its action as a tranquilizing or sedative agent in animals was found to be related directly to its depleting the brain of serotonin and not to its own presence (or absence) in the brain Various synthetic analogues of serotonin particularly the benzyl analogue of serotonin (BAS) have been found to have antiserotonin activity Of various preparations tried only BAS was suitable for long term oral use in hypertensive patients The starting dose of BAS is 12 5 mg 1-4 times a day average dose 25 mg 4 times a day and maximum dose 50 mg 4 times a day Higher doses usually cause intolerable sedation

A new oral diuretic chlorothiazide (Diuril®) was found to have hypotensive properties It is more effective as a hypotensive agent when given with other drugs than it is alone However some of the less desirable hypotensive agents can be reduced or even omitted when chlorothiazide is used as an adjunct

Chlorothiazide alone had a definite hypotensive effect in 9 of 17 hypertensive patients Reductions in blood pressure ranged from 20 systolic 10 diastolic to 60 systolic 30 diastolic

(average 21 systolic 12 diastolic) Chlorothiazide added to other antihypertensive drugs reduced the blood pressure in 19 of 23 patients with reductions ranging from 20 systolic 10 diastolic to 60 systolic 30 diastolic (average 32 systolic 21 diastolic) Most patients who responded to chlorothiazide were not in congestive heart failure did not lose weight and were taking a regular salt diet However restriction of salt appeared to increase markedly the antihypertensive effect of chlorothiazide in some patients On the other hand chlorothiazide added to a regimen of other antihypertensive agents was more hypotensive than simple salt restriction added to the same regimen

The starting hypotensive dose of chlorothiazide is 125 mg average dose 250 mg and maximum dose 500 mg 3 times a day The drug has few side effects but in larger doses can cause weakness dizziness or lassitude and in large single doses can produce gastric irritation associated with epigastric and substernal burning Occasionally it lowers serum potassium and rarely serum sodium content

► [It would appear that the favorable action of this drug is due to its effect on the excretion of sodium Of the various new antihypertensive drugs chlorothiazide is the one which appears most likely to be free of untoward effects However in patients with severe hypertension it is not likely to be effective alone but appears to potentiate the activity of the more potent and somewhat older drugs —Ed ]

**Potentiating Effect of Chlorothiazide (Diuril®) in Combination with Antihypertensive Agents Preliminary Report** Edward D Freis and Ilse M Wilson[6] (Washington D C ) studied 34 patients who had sustained hypertension Chlorothiazide was given in addition to previous treatment in doses of 1 5 Gm daily for 3 5 days then as a maintenance dose of 1 Gm daily

Of 22 patients who had been receiving ganglionic blocking agents 19 could reduce the dosage and in some the blocking agents could be discontinued The antihypertensive activity of reserpine hydralazine and veratrum or combinations of these were potentiated No side effects occurred which could be attributed to chlorothiazide There was no evidence of salt depletion However the drug is potent and can produce serious electrolyte depletion

Chlorothiazide is an important addition to antihypertensive therapy Most patients with hypertension can be controlled on a combination of chlorothiazide with 0.25 mg res

(6) M Ann D tract f Col mb 26 468 September 1957

erpine and 100 200 mg hydralazine daily or similar doses of reserpine and small subemetic doses of veratrum

**Pheochromocytoma** Review of the Literature is presented by Dale B Watkins (US Naval Hosp Philadelphia) The pharmacologic properties of norepinephrine are known since 1910 but not until 1949 was the presence of epinephrine and norepinephrine demonstrated in pheochromocytomas The tumors reported have varied from 5 to 2 000 Gm in weight and from 1 to 12 cm in diameter Usually the tumors are encapsulated reddish brown to yellowish of spherical or oval shape and are made up of ne ts or cords of cells usually of polyhedral shape strongly resembling those of the adrenal medulla Pheochromocytomas are relatively rare although over 300 cases have been reported The sex ratio is equal and they usually appear between age 20 and 50 About 90% originate in the adrenals most commonly on the right side but they may arise from various sites in the abdomen and thorax

Signs and symptoms may be progressively severe and more frequent over several weeks to many years There may be palpitation anxiety precordial distress a sensation of numbness or constriction of the extremities a feeling of fullness in the neck or throbbing in the head blurred vision dilatation of the pupils breathlessness sweating headache restlessness pain in the flanks abdomen or extremities epigastric distress colic nausea vomiting vertigo tremor prostration or semiconsciousness and cerebral vascular accidents may occur The attacks usually are rapid in onset with gradual disappearance of symptoms lasting several minutes to many hours and most often occur at night or early morning The attacks may be incited by emotion posture changes pressure on the tumor site a heavy meal physical effort prolonged fasting gargling shaving sneezing urinating trauma or any cause of hypotension There often is an initial flush followed by circumoral pallor or pallor of the extremities or other peripheral vascular phenomena Cyanosis pilomotor activity profuse diaphoresis hypertension and tachycardia have been reported

Renal displacement may be shown by intravenous or retrograde urography In selected cases extraperitoneal pneumography may show the site Elevated fasting blood sugar

(7) J Ch D 6 510 527 N mber 1957

levels and abnormal glucose tolerance curves are common and the basal metabolic rate often is elevated

Pharmacologic tests for pheochromocytoma cause pressor or depressor responses Histamine is the most useful of the drugs that induce pressor responses Apparently it liberates epinephrine by stimulating the adrenal medulla directly This test is used in patients in whom resting blood pressure does not exceed 150/110 It always is preceded by a cold pressor test to establish comparative responses for the two procedures Barbiturates and other sedatives inhibit response of the cold pressor test but not the histamine test and a test may erroneously be considered positive In testing the patient rests in a quiet room for half an hour to establish base line blood pressure 5% glucose in water is given intravenously and pressures recorded until stable Then 0 025 0 05 mg histamine is rapidly introduced through the infusion and the pressure recorded at 1 minute intervals for 15 minutes When systolic rise is 60 mm Hg or more and the diastolic 30 mm or more within 1–4 minutes returning to preinjection levels at 5 15 minutes or more the test is considered positive provided the elevation exceeds the cold pressor response Phentolamine (Regitine®) a potent relatively nontoxic adrenergic blocking agent should be at hand for intravenous administration should pressor response reach dangerous levels In absence of uremia or if the patient is not receiving sedatives or antihypertensive therapy positive response is strongly suggestive of pheochromocytoma After establishing a suitable control period 5 mg is given intravenously and when systolic pressure drops more than 35 mm and diastolic more than 25 mm within 2 minutes of injection the test is positive

Estimation of urinary excretion of catechol amines probably is the surest method for substantiating or refuting the diagnosis Estimating blood levels of epinephrine and norepinephrine does not seem practical

The only definitive treatment is removal of the tumor or tumors During surgery the team of physicians must be prepared for crises related to discharge of norepinephrine severe hypertension acute cardiac failure shock adrenal apoplexy or cardiac arrhythmias Tumor removal almost invariably precipitates profound hypotension requiring norepinephrine often in enormous amounts The rate of ad

ministration of the norepinephrine infusion will be indicated by blood pressure response and other signs

**Present Day Diagnosis and Treatment of Pheochromocytoma Review of 51 Cases** is presented by Walter F Kvale Grace M Roth William M Manger and James T Priestley[8] (Mayo Clinic and Found ) Half the patients were classed as having paroxysmal hypertension All had spells of headache usually extremely severe and most had sweating palpitation tachycardia anxiety nervousness pallor or flushing of the face nausea and vomiting pain in the chest and abdomen pain and numbness in the legs and tingling and coldness of the hands and feet Duration of illness varied from 6 weeks to 10 years Frequency of attacks varied from 10 25 daily to only 1 in 2 3 months usually lasting only 10 15 minutes Increase in frequency but not in severity was usually a differentiating point from migraine

Patients who had persistent hypertension described increasingly severe headaches excessive perspiration nervousness palpitation tremulousness and loss of weight All were thin If the condition were unrecognized disorders due to secondary vascular damage such as loss of vision coronary occlusion cerebrovascular thrombosis and congestive heart failure might be the chief symptoms

The BMR was helpful in making the diagnosis of pheochromocytoma in 6 patients with paroxysmal hypertension and in 18 with persistent hypertension Hyperthyroidism was not demonstrated in any of these patients Blood sugar was 120 mg /100 ml or more in 10 patients Excretory urograms helped locate the tumor in 10 cases Aortograms perirenal injections of air and presacral injections of oxygen were not attempted since localization preoperatively was not considered mandatory

The most useful pharmacologic tests are the histamine or phentolamine (Regitine®) tests depending on whether the blood pressure is elevated or not If a patient is normotensive 0 05 mg histamine base in 0 5 ml isotonic sodium chloride is injected rapidly intravenously The test is positive if blood pressure rises significantly with a maximum at the end of 2 minutes above the level reached in the cold pressor test If hypertension is sustained 5 mg phentolamine is injected rapidly intravenously The test is consid

(8) J A M A 164 854 861 J ne 22 1957

ered positive if the pressure decreases more than 35 mm Hg systolic and 25 mm diastolic from the basal level and remains decreased 3-4 minutes

Chemical quantitation of pressor amines in the blood is the most direct and accurate clinical method for diagnosis of pheochromocytoma However the tumor must be secreting epinephrine or arterenol spontaneously or the sample must be collected at the height of the blood pressure response to histamine Otherwise a normal value does not exclude the diagnosis of pheochromocytoma Other conditions may elevate the pressor amines (renal insufficiency jaundice increased intracranial pressure and lymphoma) and a false diagnosis may be made if this test alone is relied on

Pheochromocytomas though rare can be detected in many cases by careful history examination and the use of the histamine or phentolamine test or both If there is any question the pressor amines in the blood should be determined at the time of the highest blood pressure The tumors are peculiar to thin people Patients with hypertension who are young thin have lost weight and have hypermetabolism without hyperthyroidism should have the test

The tumors are usually benign Removal may prevent secondary vascular changes They can be malignant and can recur Therefore the diagnosis and removal of a pheochromocytoma does not always imply a promising outcome The tumors can be anywhere in the abdominal cavity Localization preoperatively is not necessary since the anterior abdominal approach allows free exploration After removal patients should be examined frequently for recurrence or metastasis If either occurs further surgery or x ray therapy may prolong life

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## THE KIDNEY

**Congenital Disorders of Renal Tubular Function** are discussed by Harold E Harrison[9] (Johns Hopkins Univ ) In nephrogenic diabetes insipidus the renal tubule does not respond to the antidiuretic hormone of the posterior pituitary Affected infants have polyuria and are unable to toler

(9) I s d M d 2 261 68 S ptembe 1957

ate water restriction from birth The characteristic biochemical change is hyperelectrolytemia i e loss of water in excess of electrolyte so that the concentrations of sodium and chloride in the serum are elevated Nephrogenic diabetes insipidus is distinguished from true diabetes insipidus by failure of response to Pitressin® injection

In renal glycosuria there is inadequate tubular reabsorption of glucose from the glomerular filtrate causing glucose to be found in the urine when its concentration in the plasma is normal This is probably a hereditary abnormality Since the defect produces no serious physiologic disturbance it may go undiagnosed and be discovered only on routine urine examination

In renal glycosuria and aminoaciduria all the amino acids occurring in plasma are excessively excreted in the urine Patients have no obvious physiologic disturbance aside from the urinary abnormalities

Essential renal cystinuria is a hereditary renal tubular defect of reabsorption of cystine lysine arginine and ornithine which appear in the urine in excessive amounts The clinical manifestations are only those of precipitation of cystine calculi Formation of stones can be minimized by administration of alkalinizing salts

In cystine storage disease or cystinosis renal tubular reabsorption of phosphate is deranged along with other tubular functions and hypophosphatemic rickets occurs This is a rare and grave metabolic disorder and must be distinguished from renal cystinuria which is a comparatively benign error of tubular metabolism Cystinosis is familial Affected infants appear normal at birth and may show no untoward effects during the first few months of life The usual symptoms are failure to thrive poor weight gain slow growth muscle weakness and lassitude Patients can be treated by vitamin D 25 000 50 000 units daily which increases phosphate retention elevates the concentration of serum phosphorus and causes healing of the rachitic and osteomalacic lesions in the bone

The triad of renal glycosuria aminoaciduria and phosphaturia associated with hypophosphatemic rickets and osteomalacia is usually referred to as the Fanconi syndrome In infancy cystinosis is the most important cause of this syndrome but the disorder is found in older children and

in adults without any evidence of cystine deposit in tissues

Tubular dysfunction in congenital renal tubular acidosis is believed to be a failure of the mechanism for the formation of acid urine by exchange of the H ion of the tubular cells for the cations Na K Ca and $Mg^+$ in the tubular contents The urine excreted is neutral or alkaline though the diet provides an excess of acid over base Consequently a metabolic acidosis develops and is manifested by reduced serum bicarbonate concentration and reciprocal elevation of the concentration of serum chloride The earliest clinical manifestations are growth retardation lack of weight gain and polyuria If no definitive treatment is given the skeletal changes of rickets appear by the end of the first year of life and severe skeletal deformities may develop

**Diseases of Renal Tubules in Childhood** are reviewed by Carolyn F Piel[1] (Stanford Univ ) Renal glycosuria is diagnosed when glucose is present in the urine at all times in fasting as well as in postprandial states and is relatively uninfluenced by intake of carbohydrate or administration of moderate amounts of insulin Fasting blood sugar concentration is normal as is the glucose tolerance curve Carbohydrate metabolism is normal as indicated by the respiratory quotient and decrease in concentration of inorganic phosphorus in the serum after ingestion of glucose Renal glycosuris produces no symptoms except polyuria and polydipsia at times and occasionally ketonuria and diaper rash in young infants The defect is a low threshold for glucose Glomerular filtration rate and renal plasma flow are normal but evidence about abnormalities in tubular function is conflicting Renal glycosuria is inherited probably as a dominant characteristic

Renal diabetes insipidus has been described as characterized by polyuria polydipsia vomiting dehydration resistant constipation unexplained fever and failure to grow In one series of 6 cases in the literature only males were affected 3 of whom were half brothers and symptoms began shortly after birth In another report on 7 cases in 5 generations of 1 family the disease occurred only in males and appeared to be a sex linked recessive characteristic Only 1 case has been reported in a female Vasopressin has no effect and the amounts of vasopressin in the serum are normal Hyper

(1) Ped t 20 337 3 7 \ g t 195

tonic saline infusion produces no antidiuretic response All evidence indicates that this is a functional disturbance in which normal renal tubules fail to respond to adequate amounts of vasopressin Treatment consists of adequate hydration and nutrition Prognosis is uncertain Too few cases have been followed to predict the eventual outcome

Cystinuria a recessive hereditary abnormality which rarely is symptomatic is due to reduced tubular reabsorption of cystine and other amino acids Excessive amounts of cystine are excreted when methionine or cystine are given orally Renal tubular reabsorption of the unnatural d i omer of cystine is much less than the naturally occurring l isomer which is evidence of deficiency in the tubular transport mechanism

Renal hyperchloremic acidosis is now recognized in all age groups as primarily a tubular disease characterized by increased serum chlorides decreased plasma bicarbonate and an alkaline urine In the infantile type symptoms of anorexia vomiting polyuria hypotonia constipation and failure to thrive begin usually in the first 18 months The urine is dilute and does not concentrate after vasopressin Decalcification of bone and nephrocalcinosis have occurred In older children the disease is characterized by stunted growth rickets polyuria and polydipsia The cause of the disease is not known If it is unrecognized most afflicted infants will die A few apparently recover without therapy but most require excess alkali at least temporarily In older children adequate amounts of Shohl s solution (sodium citrate and citric acid) relieve the biochemical changes and heal the rickets and growth ensues Nephrocalcinosis polyuria and polydipsia persist Adults respond similarly

Rickets resistant to vitamin D has been recognized since adequate intake of vitamin D has become general and is not rare The first signs usually appear within the first 2 years Despite usually adequate intake of vitamin D and adequate nutrition florid rickets develops with pseudofractures crippling deformities and stunted growth Serum calcium may be normal or decreased alkaline phosphatase increased and phosphorus extremely low This form of rickets differs from simple deprivational rickets only in lack of response to vitamin D There is a strong familial tendency Symptoms respond to excessively high doses of vitamin D some patients

improve with sodium citrate and citric acid solution The cause is unknown but there is evidence that the fundamental abnormality is within the tubule causing decreased absorption of phosphate and secondary hyperfunction of the parathyroids Severity of the disease is variable prognosis seems to depend on the degree of severity rather than on adequate medication

The Fanconi syndrome which is hereditary consists of renal glycosuria hypophosphatemic rickets or osteomalacia generalized aminoaciduria and occasionally vasopressin-resistant polyuria and hyperchloremic acidosis The infant or young child is severely affected and fails to thrive in the 1st year of life Polyuria polydipsia vomiting lethargy and constipation usually are present with frequent unexplained pyrexia Unexpected death may occur acutely presumably due to hypopotassemia Older children are stunted have rickets and occasionally photophobia Many have impaired liver function As the disease progresses kidney function gradually is lost As glomerular filtration diminishes hyperphosphatemia results and the rickets heals However azotemia and death eventually ensue Almost all children have cystinosis Progressive destruction of renal tissue during the course of the syndrome has been well established but pathogenesis is unknown The most frequently considered etiologic factors are the toxic effects of amino acids and altered pH on renal cells Therapy with adequate alkali and vitamin D greatly improves the patients Clinical improvement may follow therapy with vitamin D Patients have not been followed long enough to determine whether dwarfism and renal failure can be prevented

**Percutaneous Transfemoral Selective Renal Arteriography (Including Cineradiology)** a safer more accurate technic is described by *D McC Gregg J M Allcock* and *F R Berridge*[2] A quantity and concentration of contrast medium can be injected which even if misdirected causes no damage This method avoids the disadvantages of need for high injection pressure there is no masking of renal vessels by unwanted and unnecessary filling of other vessels and use of a test injection usually can be omitted so that there is no contrast medium present in the calyces or pelvis when the main injection is made

( ) B t J R d 1, 30 423 435 A g t 1957

TECHNIC —A radiopaque catheter size PE 160 is shaped in hot water into the required curve The distal end is smoothed and slightly tapered and side holes are bored near the tip A small distal curve is shaped that runs across the aorta and a shallow longer more proximal secondary curve that runs down the aorta and acts as a spring that pushes the tip of the catheter against the aortic wall The catheter is 50 cm long with capacity of 1 cc Urografin is the most satisfactory medium in a strength of 38%

The patient is prepared with colonic lavage and laid supine on a polyfoam mattress on the cassette tunnel which is covered by a lead sheet in the center of which is a circular hole 9 in in diameter The skin is painted with iodine local anesthesia is injected around the femoral artery just below the inguinal ligament opposite the kidney to be investigated the needle is introduced into the femoral artery and the catheter threaded up the needle When the tip is estimated to have just passed the level of the renal artery screening is begun and the guide wire is removed The catheter is readily visible through the image intensifier even in thick patients the ordinary screen can work only in thin patients The tip is directed toward the desired kidney and placed above the renal artery as it is pulled down it engages in the orifice and moves outward When the catheter is correctly placed an injection of 10 ml saline should cause no pain If there is still doubt a film can be taken as 1 ml contrast medium is injected When all is ready 8 ml 38% Urografin is taken into a syringe and injected steadily but slowly in about 1½ seconds and six 12×10 in films are taken as rapidly as possible Further injections may be given with the patient in oblique position if necessary and a cinematograph film taken if wanted

Accessory renal arteries may be catheterized by this method

**Recognition and Treatment of Renal Arterial Stenosis Associated with Hypertension** in 7 patients are reported by Paul T DeCamp and Robert Birchall[3] (Ochsner Clinic) In recent years it has become increasingly apparent that hypertension in man may be due to renal artery stenosis A renal humoral mechanism is at least in part responsible The contralateral kidney is exposed to the full effects of the hypertension Blood flow through the two kidneys as ordinarily measured may be equal Renal function presumably is normal and equal on both sides except when stenosis is severe which then causes atrophy Usually as in coarctation of the aorta systemic hypertension drives sufficient blood past the stenosis to permit adequate renal nourishment and function on the involved side On the other side intrarenal arteriolar spasm prevents excessive blood flow and maintains normal blood flow The kidney on the side of the stenosis is com

(3) S ge y 43 134 152 J ua y 1958

pletely protected from the hypertension Necrotizing arteriolitis may develop in the contralateral kidney exposed to the hypertension Removing the stenosis or the kidney involved may restore considerable function to the contralateral kidney But unless renal ischemia on the involved side is extreme with secondary fibrosis and atrophy this kidney may be the better kidney For this reason conservative surgery is most rewarding If only one kidney or part of one kidney lies distal to an arterial stenotic lesion systemic hypertension may develop

Symptoms and signs are those of any type of severe hypertension and progress rapidly The diastolic levels generally are fixed and high Headache malaise and visual disturbances develop and heart and renal failure may supervene Renal function characteristically remains normal until the process advances Excretory urograms are normal unless infarction or complete loss of renal function has occurred

Diagnosis often is difficult Renal arteriography is of definite value It is indicated in all patients in whom hypertension developed before age 25 or after age 50 and also between ages 25 and 50 when something in the history does not conform with the usual natural history of essential hypertension Unilateral renal plasma clearance may be helpful The differential determination of urinary sodium and potassium is unreliable

At operation diagnosis is confirmed by significant drop in arterial pressure across the stenotic segment If possible arterial reconstruction with conservation of the kidney is indicated because the latter often is normal and may well be the better of the two kidneys The patient s own vessels usually can be used for end to side anastomosis with the splenic artery on the left or splenectomy can be done swinging the splenic artery over to the right side When conservative surgery is impossible or the kidney is seriously damaged nephrectomy is indicated

**Aneurysm of Renal Artery** is reviewed by Anthony P Garritano[4] (Philadelphia) This lesion is considered rare but is being reported with increasing frequency with 175 cases now documented The cause may be congenital or acquired Most arteriovenous aneurysms are considered congenital The acquired lesions may be due to degeneration

(4) Am. J S g 94 638 648 O t be 1957

inflammation or trauma Arteriosclerosis is a factor in relatively few cases inflammation is infrequent and trauma was a factor in only a few

Complications include various degrees of renal changes secondary cardiovascular abnormalities and rupture of the aneurysm with subsequent hemorrhage Compromise of renal vascular supply may lead to renal ischemia with various stages of atrophy and hypertension In 5 patients hypertension was relieved by nephrectomy Symptoms and signs vary with the size and type of lesion and may include pain tenderness hematuria hypertension and presence of a mass bruit or palpable pulsation Small aneurysms may be asymptomatic Hematuria is present in about one third varying from profuse to minimal Diagnosis may be difficult The most reliable signs include calcification in the renal area on x ray study and the presence of a suspicious bruit thrill or palpable pulsating mass Abdominal arteriography may be helpful

The only treatment is surgical in most cases nephrectomy Once the aneurysm is diagnosed prompt surgery is imperative The function and condition of the opposite kidney should always be evaluated first Almost all untreated patients die mostly of hemorrhage in contrast to only 14% of those who have had surgery Only 4 5% of those who had nephrectomy died and operation was lifesaving in many instances Aneurysm of the renal artery is an important lesion It always should be considered in patients with unexplained hypertension or hematuria

**Bilateral Polycystic Disease of Kidneys Follow up of 284 Patients and Their Families** is reported by O Z Dalgaard[5] (Copenhagen) Polycystic kidneys are those in which the tissue is replaced by many closely packed cysts It is the most important of the cystic diseases of the kidney At autopsy frequency of polycystic kidneys in adults is 1 773 Incidence rises by age groups until age 30 thereafter remaining stationary The malformation appears so rarely in children that it must be considered as a curiosity The most important etiologic feature must be hereditary but pathogenesis is unknown Of 211 nearest family members who had intravenous urography 27 had polycystic kidneys and 19 were suspected of having polycystic kidneys

(5) Acta med. sca d n ( pp 3 8) 158 1 255 195

Pain and vague abdominal symptoms were common and in 59% were the earliest symptoms Renal colic and possible passage of renal calculi occasionally occurred Hematuria was common (45%) and uremia occurred often in the terminal stage Cardiovascular symptoms including hypertension were frequent and began late in the course of the disease Kidney tumors were palpable in 61% and proteinuria was noted in 75% Pyuria and bacteriuria usually began half way through the course of the disease in 46%

At autopsy on 173 patients with polycystic kidneys from one to several liver cysts were found in 16% and 21% had many cysts In 14 families 1 or more persons had polycystic kidneys and polycystic liver indicating an etiologic relationship between polycystic kidneys and polycystic liver In 7 patients who died subarachnoid hemorrhage was found *at autopsy which is significantly higher than the number* expected in the general population A common cause is not definitely proved but appears to be likely Perhaps a single gene is the cause of the syndrome of malformations namely polycystic kidneys polycystic liver and congenital aneurysm of the basal arteries of the brain Statistical analysis indicates no sex linkage neither complete nor partial There probably are at least two forms of congenital polycystic kidneys enlarged spongy kidneys with recessive inheritance and hypoplastic cystically converted kidneys which perhaps is not genetically determined

Curative therapy is not available Families of patients who have polycystic kidneys should not be traced for the purpose of offering them help Preventive medicine offers two possibilities use of negative eugenic measures by hindering transmission of the gene for polycystic kidneys from generation to generation or restricting preventive medical treatment to the patient

**Uric Acid Calculi** according to Russell E Alfyn[6] (Harrisburg Pa ) are more common than generally supposed Diagnosis is easy once these calculi are considered and treatment is highly gratifying to patient and physician Four clinical groups can be delineated In group 1 the criteria are recurrent typical renal colic associated with discovery by cystoscopy of golden crystals or gold sand in the bladder elevated blood uric acid content normal intravenous

(6) J U L. 78 314 317 O t be 1957

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(5) Acta med. scand v ( pp 3 8) 158 1 255 1957

Excessive oxalate and calcium in the urine does not necessarily lead to precipitation of the crystals Magnesium vitamins A and D urea colloids and certain acids may prevent precipitation of calcium oxalate and if deficient may be a factor in the disease

The symptomatology although characteristic is not specific Urinary calculi develop and usually the illness is of long duration ranging from 3 weeks to 19 years Laboratory findings in late stages are characteristic of renal failure with nitrogen retention low serum calcium levels and elevated serum phosphorus levels in most instances Alkaline phosphatase in most patients was normal Anemia was a common late finding

Crystals were found obstructing the tubules in each patient with compression and atrophy of the tubular epithelium and often extended into interstitial tissues evoking mild chronic inflammation Glomeruli were unaffected The crystals yellow birefringent and round with a radial rosette like pattern also were found in bone the heart spleen liver and thymus thyroid testis lung adrenal pituitary pancreas and parathyroid

Diagnostically few if any characteristics distinguish oxalosis from other conditions leading to nephrolithiasis Therapy is empiric Foods rich in oxalate should be restricted adequate urine volume should be insured and adequate vitamins A and D taken The value of acidification or alkalinization of body fluids is unproved The presence of magnesium helps to prevent precipitation of calcium oxalate

**Study of Magnesium Metabolism in Acute Renal Failure Employing Multichannel Flame Spectrometer** Magnesium is second only to potassium in intracellular abundance and the total is estimated at 20 Gm in the human body Until now measurement of magnesium has been protracted or inaccurate or both but a flame spectrophotometric method allows simple and precise determination of magnesium in serum Warren E C Wacker and Bert L Vallee[8] (Harvard Med School) report findings in 14 normal subjects and 12 with renal disease

The clinical picture of magnesium intoxication consists in muscular weakness somnolence and coma similar to that of uremia It has been noted that the severity of potassium

(8) New Engl J Med 257 1254-126 Dec 26 1957

urogram and normal retrograde pyelogram and complete relief of symptoms with appropriate therapy In group 2 symptoms have progressed until the ureter is plugged with uric acid crystals and debris and the kidney does not function In group 3 definite calculus is present that produces a filling defect The calculus may pass spontaneously or require surgery Group 4 is similar to group 3 except that blood uric acid is normal

Differential diagnosis includes papillary carcinoma of the *renal pelvis polycystic kidney disease without gross* deformity clear cell carcinoma of the kidney with extension to the renal pelvis organized blood clot in the renal pelvis precalcareous matrix pure cholesterol calculus and primary carcinoma of the ureter

Treatment consists of surgical removal of the stone when necessary high fluid intake sodium bicarbonate and Benamid® by mouth

**Idiopathic Familial Oxalosis** is an unusual form of renal calcinosis in which calcium oxalate crystals are found in renal tubules and interstitial tissue Renal parenchyma is destroyed because of deposition of the crystals, leading to renal failure and death Similar crystals may be found in other viscera and in bone David L Edwards[7] (Washington Univ ) presents the only case as yet reported of this rare disease in more than 1 adult in a single family Two adult brothers had parenchymal deposits of calcium oxalate crystals in the kidneys leading to renal damage and death in uremia Similar crystals were found in the testis of 1 and in the myocardium of both These are the 19th and 20th known cases of idiopathic familial oxalosis the second instance in which familial incidence was proved histologically and the first involving 2 adults in the same family

Despite the frequency with which oxalates are found in the urine of normal persons and the high proportion of renal stones composed of oxalates crystals rarely are deposited in the renal parenchyma The reason for this is unknown Oxalates in normal persons are believed to be ingested from coffee spinach rhubarb cocoa and some fruits A small amount may be produced endogenously Most patients with oxalosis show no evidence of excessive ingestion of oxalates Some unknown type of metabolic disorder must be present

(7) A M A A h P th. 64 546-555 N mber 1957

The transplanted kidneys functioned normally in most respects The one major abnormality was decreased glomerular filtration rate and renal plasma flow in initial studies after transplantation Ultimately these values equaled those of the normal kidney The filtration rate of the denervated kidney was less than the simultaneous value of the intact organ However sodium excretion also was less and the ratio of sodium excretion to filtered load was not greater in the transplanted kidney in fact in several experiments the rates were less

When extracellular fluid volume was expanded by infusion of 3% saline each kidney elaborated a sodium rich urine Tubular reabsorption by the transplanted kidney was normal when the animal was unanesthetized and the decrease during anesthesia was attributable to concurrent changes in glomerular filtration When the glomerular filtration rate of the intact kidney decreased more than that of the transplanted kidney the latter excreted more sodium When the rate decreased more in the transplanted kidney excretion was less than that of the intact kidney

The results suggest that complete denervation induces no consistent abnormality in tubular transport of sodium chloride Previous studies in which it was reported that denervated kidneys excrete more sodium neglected the slightly greater filtration rate that also was present

**Experimental Aminonucleoside Nephrosis in Rats** The nephrotic syndrome is characterized by proteinuria hypoalbuminemia hyperlipemia and edema In man it is associated with glomerulonephritis amyloidosis diabetes mellitus and lupus erythematosus and occurs after trimethadione administration Experimental nephrosis in rats can be produced by injection of antirat kidney serum or by 6 dimethylaminopurine 3 amino d ribose Eugene B Fiegelson John W Drake and Lillian Recant[1] (Washington Univ ) studied the nephrosis that was induced by the latter drug

Injections uniformly induced nephrosis in all animals The first manifestation was proteinuria then accumulation of ascites No animal survived 17 days though injections were stopped Urine examinations revealed proteinuria ho

(1) J Lab & Clin Med 50 437 446 Sept mb 1957

intoxication cannot always be correlated with the concentration of potassium in serum Since the clinical and ECG abnormalities of hyperkalemia and hypermagnesemia are similar hypermagnesemia may in part explain some of the symptom complex usually considered as potassium intoxication

Duplicate magnesium analyses of the normal serums ranged from 1 75 to 2 56 with a mean of 2 05 mEq/L All patients studied during the oliguric phase of acute renal failure had a markedly elevated serum magnesium concentration 2 9-4 81 with a mean of 3 81 mEq/L In most the elevation of serum magnesium concentration paralleled the increase in potassium concentration With hemodialysis in the artificial kidney serum magnesium concentration decreased in each case

It is difficult to single out the specific clinical effect of this altered magnesium metabolism since it occurs as part of a complex syndrome with major disturbances of all other ions in the serum The increase in magnesium concentration in the serum of patients with uremia undoubtedly contributes to the clinical picture of this disease Owing to marked similarities of the ECG changes associated with hyperkalemia and hypermagnesemia those due to the latter are often mistaken for those of hyperkalemia Hypermagnesemia may account for the symptoms diagnosed as due to hyperkalemia in the presence of normal serum levels of potassium and may explain the clinical manifestations of uremia which are pronounced and out of proportion to the concentrations of nitrogenous waste products

**Functional Capacity of Kidney Denervated by Autotransplantation in Dog** The influence of renal nerves on the renal tubular transport of sodium chloride has been controversial for years A kidney transplanted from one identical twin to another and totally denervated at the time was shown to function normally To explore this problem further Neal S Bricker Ralph A Straffon Edward P Mahoney and John P Merrill[9] (Boston) autotransplanted in 6 dogs one kidney from the renal fossa to the iliac fossa The opposite kidney served as the control Permanent hemibladders were constructed allowing simultaneous and serial study of the functions of both kidneys

(9) J Clin I e t 37 185 197 F bru ry 1958

who had proteinuria but only minimal hypoalbuminemia hyperlipemia and edema

A diet of 200 mg sodium and 2 3 Gm potassium was prescribed throughout steroid therapy Intermediate feedings and in most adults aluminum hydroxide were also given Children were given prophylactic penicillin 250 000-500 000 units daily by mouth during treatment and for 6 months to a year after remission Antibiotics in adults were used only on specific indication After 2 weeks to 2 months observation in the hospital patients were given 40 mg prednisone (or 150 200 mg hydrocortisone) daily by mouth in 4 divided doses This was continued until the maximum change in levels of proteinuria or serum albumin occurred in most cases at least 1 month

Complete remission during steroid therapy with complete clearing of proteinuria occurred in 6 patients Thereafter serum albumin began to rise reaching normal levels within 30 days Serum cholesterol fell gradually toward normal as serum albumin rose In 6 other patients residual proteinuria remained though it dramatically decreased In 4 patients some albumin persisted in the urine and some hypoalbuminemia remained In the other 5 patients urine and serum proteins were unchanged but the patients became free from edema after a significant diuresis when the steroid was stopped

Quantitative determination of 24-hour urine protein is the most sensitive and satisfactory method for following the day to day course of patients with the nephrotic syndrome particularly for recognizing remissions and exacerbations When a patient is sent home in complete remission the first morning specimen of urine is tested daily with a protein precipitating agent Thus a relapse is accurately documented and appropriate therapy immediately started When a relapse occurs onset of proteinuria is followed by a fall in serum albumin and increase in serum lipids and erythrocyte sedimentation rate and often by an increase in body weight

The dose required varied from patient to patient but most responded to about 40 mg prednisone daily None of the 5 patients who did not respond to this dose did so to any higher dose In most cases a given dose was completely ineffective or maximally effective

Therapy is initiated in adults and children with 40 mg

mogeneous and granular casts and a few white blood cells Administration of cortisone did not favorably affect the course of the disease

Proteinuria began between the 6th and 8th day of injections usually becoming massive by the 10th day Albumin appeared in the urine first followed later by alpha beta and gamma globulins Hypoproteinemia appeared after several days of proteinuria Albumin levels decreased whereas alpha$_2$ globulin increased markedly—changes similar to those seen in human nephrosis Cortisone treatment had no effect on these abnormalities

The concentration of serum cholesterol increased *significantly as the syndrome progressed being correlated with the decrease in serum albumin Serum nonprotein nitrogen rose progressively without oliguria in all animals* Liver glycogen was uniformly lower in the nephrotic animals No significant differences in adrenal gland weight or quantitative steroid formation could be demonstrated between control and nephrotic animals

All tissues examined were edematous and pale Ascites and hydrothorax were present Microscopic changes were nonspecific in the glomeruli consisting of a frayed appearance of the basement membrane and general fulness of the glomerular tuft Some Bowman capsules appeared distended Casts were seen in the tubules and fat staining material in tubular epithelium

*The mechanism of aminonucleoside nephrosis is unknown It probably produces profound enzyme* aberrations since there was so little evidence of morphologic change Further investigation is underway to examine its potential role in metabolism

**Nephrotic Syndrome Clinical Observations on Therapy with Prednisone and Other Steroids** This syndrome of massive proteinuria edema hypoproteinemia and hyperlipemia may occur in many different diseases Diabetes mellitus lupus erythematosus amyloidosis syphilis *malaria* and renal vein thrombosis are known causes but *most cases have no recognizable etiology* and are classed as *idiopathic* Howard C *Goodman* and James H Baxter[2] (Nat l Inst of Health) *report* the effect of prednisone and hydrocortisone in 20 patients with the complete nephrotic syndrome and 3

(2) J A M A 165 1798-1808 Dec 7 1957

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prednisone (or 160 mg hydrocortisone)/day in 4 divided doses and continued at least 3 weeks When remission occurs the dosage is continued until no further decrease in proteinuria or increase in serum albumin ensues and is then gradually reduced and discontinued If proteinuria recurs therapy is reinstituted and continued until a second remission Therapy is adapted to the needs of each patient in preference to the use of a rigid schedule of short or long term therapy Prolonged maintenance therapy is unjustified

The age of the patient is of no help in predicting response to therapy Three fourth of children and of adults responded Apparently in terms of response the idiopathic nephrotic syndrome is fundamentally the same disease in children and adults Microscopic hematuria and moderate renal insufficiency did not necessarily preclude a good response

No essential difference in effectiveness or side effects was noted between prednisone and hydrocortisone The usual side effects of facial rounding changes in fat deposition hirsutism acne papular erythematous rash increased appetite euphoria and a feeling of nervous tension were noted One patient acquired a bleeding duodenal ulcer and several had mild gastrointestinal symptoms

**Treatment of Nephrotic Syndrome with Steroids in Children and Adults** Nephrotic syndrome usually refers to the so called pure or lipid nephrosis and to the nephrotic stage of chronic glomerulonephritis Most likely it is the result of an antigen antibody reaction in which large amounts of complement are used Of 61 patients studied by Kurt Lange Ruth Strang Lawrence B Slobody and Eugene J Wenk[3] (New York Med College) 87% had low serum complement levels although the levels may be normal in mild cases or at the beginning and end of the disease The nephrosis is probably a distinct disease an immunologic disorder characterized by a complement binding antigen antibody reaction producing functional and if persistent morphologic tissue damage Probably other capillaries besides the glomerular have increased permeability

Corticotropin and cortisone depress the formation of certain antibodies When corticotropin was given to 42 children and 19 adults with the nephrotic syndrome 82 and 68% respectively had complete diuresis The others had complete

(3) A.M A Arch Int M d 99 760 770 May 1957

diuresis when corticotropin therapy was repeated Diuresis was always preceded by a rise in complement if this did not occur neither did diuresis If not further treated after the initial diuresis half the patients had recurrence of nephrosis in 6 months and two thirds in 12 months When cortisone was given on 3 successive days of each week for 1 year after initial diuresis the mortality in the 24 cases observed was reduced from the expected 5 6 deaths to the observed 1 death Proteinuria is rapidly reduced when patients are on maintenance therapy Blood chemistry quickly returns to normal By the end of 1 year of maintenance therapy 61% of the patients had no proteinuria

Diuresis can be induced with corticotropin 100 200 units daily for 10 20 days depending on the severity and duration of the disease Antibiotics are given during treatment If the first course fails a second with larger doses for a longer period should be given Five days after onset of diuresis oral cortisone (300 mg daily to children under 40 lb 400 mg daily to all others) is given on 3 successive days each week Maintenance therapy should not be started unless diuresis is complete Oral antibiotics and 1 2 Gm potassium chloride may be prescribed The dose of cortisone should not be reduced nor the interval between courses extended for a full year The dose is then tapered Growth and development are not impaired by this prolonged intermittent steroid therapy Children and adults respond well Therapy should be started as early as possible in the disease since results are then decidedly better

► [This and the preceding abstract indicate the importance of this relatively new form of therapy Obviously the patient should be observed carefully for evidence of infectious disease including tuberculosis Since peptic ulcer occasionally occurs as a complication it is probably well to institute a modified ulcer regimen with 6 daily feedings and alkali as a prophylaxis in patients receiving prolonged steroidal treatment —Ed ]

**Urinary Findings Diagnostic of Pyelonephritis** George G Jackson Hans G Grieble and Kermit B Knudsen[4] (Univ of Illinois) studied the relation of preoperative urinary findings to the pathologic conditions found at operation in 71 patients who had unilateral nephrectomy for various types of renal disease Classic acute clinical pyelonephritis is easily diagnosed Fever dysuria frequency of urination and back pain with characteristic radiation are present In contrast chronic pyelonephritis is the cause of about 50% of the

(4) J A M A 166 14 17 Ja 4 1958

nephritis found at autopsy without antecedent history of recognized genitourinary disease Chronic pyelonephritis was present in 41 (58%) of the 71 resected kidneys Its frequency with various types of renal anatomic lesions was nephrolithiasis 85% hydronephrosis 83% congenial anomaly 50% carcinoma 7% and tuberculosis none Thirty (42%) of the patients had similar anatomic lesions but no pyelonephritis

Of the patients with pyelonephritis 78% had pyuria (more than 10 leukocytes/high power field in 58%) and 22% showed no leukocytes in the single preoperative urine specimen examined Of the patients without pyelonephritis 47% had no leukocytes 20% had 2 10/high power field and 33% had more than 10 The differences in incidence and magnitude of pyuria among patients with and without pyelonephritis are statistically significant but in an individual patient were unreliable Hematuria was more characteristic of the group without pyelonephritis but this was not absolute Proteinuria was present in 65% of the patients with pyelonephritis but more than half of these excreted only trace amounts

Pyuria is the hallmark of pyelonephritis and in general the degree of pyuria parallels the severity of inflammation Pyuria is not always present with pyelonephritis and when present does not always indicate bacterial infection of the kidney Pus cell casts always mean parenchymal inflammation but they are uncommon Clumps of leukocytes are common in urine from infected kidneys There is good correlation between pale staining leukocytes in the urine (using supravital stain) and presence of pyelonephritis

Hematuria with pyelonephritis should suggest investigation for tumor congenital anomaly tuberculosis urinary tract concretion embolism trauma or glomerulonephritis Proteinuria always indicates renal parenchymal involvement Excretion of large amounts is not characteristic of pyelonephritis until the far advanced or preterminal stages of the disease

Quantitative urine cultures enable identification of significant infection even when symptoms are absent Patients with fewer than 100 000 bacteria/ml may require further observation above this number infection is present Voided specimens even from females are suitable for det ng sig

nificant bacteriuria if quantitative cultures are done This is the recommended procedure for screening patients for urinary tract infection If the specific bacteria is to be determined catheter specimens are more reliable

Pyuria absence of microscopic hematuria and low degree of proteinuria are characteristic of chronic pyelonephritis but not diagnostic

**Experimental Studies on Pathogenesis of Pyelonephritic Contracted Kidney** are reported by A Thelen K Rother and H Sarre[5] (Univ of Freiburg) Experimental pyelonephritis was induced in rabbits and often a pyelonephritic contracted kidney was also produced Initiation of pyelonephritis depended on presence of an incomplete transistory urinary obstruction and inflammation The inflammation may be caused by bacterial infection due to coli bacilli or enterococci involving the renal pelvis and surrounding tissues or by an allergic toxic phenomenon after preimmunization and injection of vaccine into the renal pelvis its wall *and surroundings*

Both the urinary obstruction and early inflammation led to severe transformation and mechanical obstruction of the sensitive renal circulation which caused severe changes in the nutritive vessels of the kidneys with secondary atrophy of the parenchyma Chronic proliferative changes in the renal vessels accompanying long standing pyelonephritis further aggravated the parenchymal circulation

The first signs of a contracted kidney appeared about the 30th day after onset of inflammation and were fully developed in 3 months Occasionally contracted kidneys resulted from total and *permanent* obstruction of the ureter without dilatation of the renal pelvis The resulting macro and microscopic changes differed from those in typical pyelonephritic contracted kidneys

The authors believe that these experimental observations hold for pathology in human beings in whom pyelonephritis may undoubtedly lead to a contracted kidney Urinary retention for a short period seems to be essential Whether chronic pyelonephritis with a slow insidious course may result in a contracted kidney is not known

**Unilateral Nonfunctioning Kidney** D E Strandness Jr[6] (VA Hosp Seattle) reviewed 70 cases in 65 of which clin

(5) U f f m f δ 359 595 1956
(6) A M A Arch I t M d 101 615-619 M h 1958

ical diagnosis and cause had been established From these cases and others from the literature it was found that extra renal lesions which occasionally result in nonvisualization of one kidney usually are diagnosed by the combination of plain x ray film of the abdomen cystoscopy and retrograde pyelography Parenchymal disease whether congenital or acquired presents problems in diagnosis When kidney function is absent a normal size and architecture suggests renal artery thrombosis a kidney of small size and normal architecture without function suggests renal artery thrombosis or hypoplasia and a small kidney with abnormal architecture without function suggests atrophic pyelonephritis or *hypoplasia Aplasia or agenesis is suggested when the ure*teral orifice is missing or the trigone is absent Retrograde pyelography usually will confirm the diagnosis of neoplasm tuberculosis or congenital malformation of the pelvis and ureter Aortography may aid in diagnosing neoplasm renal artery thrombosis aberrant renal artery and agenesis Nephrolithiasis rarely is a diagnostic problem when intravenous pyelography is done for a history of abdominal pain suggestive of renal colic hematuria urinary tract infection or previous nephrolithiasis The possibility of nonopaque calculus (incidence of 2 16 5%) should be kept in mind

Clinical evaluation of a unilateral small kidney is difficult It is impractical and almost impossible to distinguish clinically or pathologically between hypoplasia and atrophic pyelonephritis It is more practical to call such kidneys atrophic kidney or renal atrophy because the cause is not apparent Emboli are the commonest cause of renal infarction Another cause is spontaneous thrombosis of the renal artery Venous thrombosis usually occurs with sepsis and often is bilateral Trauma as a cause usually is determined by history of injury and hematuria Diagnosis of tuberculosis of the genitourinary tract cannot be established without showing acid fast bacilli Neoplasms of the colon or female reproductive tract may result in nonvisualization of one kidney by extraluminal obstruction of the ureter

Peritoneal Lavage—Neglected Clinical Procedure is a simple effective therapy for severely toxic acute renal failure in the absence of an artificial kidney according to R E Hearn and Wilbur C Berry[7] (Honolulu) *Intermittent*

(7) H w M J 17 40 42 S pt O t 19[illegible]

lavage causes less infection has less tendency to pooling and channeling of fluid in the abdomen uses smaller volumes of fluid and requires simpler apparatus than does constant lavage

PROCEDURE —A polyethylene nasogastric tube is prepared by cutting 12 15 holes 2 3 mm large in the distal 10 in and soaking it for several hours in Zephiran® solution A trocar is aseptically inserted into the abdomen 1 2 in below and 2 3 in to the left of the umbilicus the obturator is removed and the polyethylene tube inserted down and to the right for 12 15 in The trocar sleeve is removed and the tube sutured securely to the abdominal wall An ordinary intravenous tube is attached to the free end of the nasogastric tube

A solution is made up of 1 000 cc of 5% dextrose in distilled water 1 000 cc of 5% dextrose in normal saline and 1 000 cc normal saline To each liter is added 45 mEq sodium bicarbonate 4 mEq potassium chloride and 100 000 units of aqueous crystalline penicillin This solution adequately maintains all the serum electrolytes except calcium This is given intravenously 10 cc of 10% calcium gluconate after each 2 dialyses Standard intravenous solution bottles fit easily on the free end of the intravenous tubing The 3 L are allowed to flow one after another into the peritoneal cavity by the force of gravity and are left undisturbed 2 3 hours Then the same bottles are filled from the abdomen by placing them on the floor and allowing them to fill by gravity

Peritoneal lavage is indicated in acute renal failure in which the blood urea nitrogen is high and rising serum potassium is 7 mEq /L and rising especially if there are ECG abnormalities CO combining power is 12 mEq /L or less or if the patient has been overloaded with water and salt early *in treatment Intoxication with bromides* salicylates or phenobarbital can be rapidly treated by lavage Contraindications are recent extensive abdominal surgery peritonitis infections of the anterior abdominal wall marked bowel distention extreme obesity of the abdominal wall and extensive adhesions *from previous surgery*

Serum electrolytes and proteins should be followed closely during treatment In edema or poisoning treatment should continue until the desired results have been obtained In renal failure therapy should continue until the blood urea *nitrogen is less than 100 mg /100 ml or until excretion* of urine exceeds 1 000 cc daily or until the urea in the urine exceeds that in the dialysate for the same 24 hours

**Use of Caval Catheterization in Cases of Severe Oliguria and Anuria** Circulatory renal insufficiency is a common *cause of oliguria due to oligemia of shock* hemorrhage and

dehydration It can usually be corrected by replacing fluids blood and electrolytes as required but if treatment is delayed tubular necrosis may result Acute tubular necrosis may result from prolonged hypotension due to hemorrhage and shock from transfusion of incompatible blood from extensive burns and crushing injuries from chemical poisons such as mercuric chloride carbon tetrachloride and phenolic substances or from bacterial toxins Prognosis is usually excellent and the aim is to keep the patient alive in as near a physiologic state as possible until the damaged tubules slowly resume normal function

J W Chambers and George Smith[8] (Univ of Glasgow) review 29 cases of acute renal failure treated during 1950-57 The essential feature of therapy is to restrict basal daily intake to about 700 ml of 50% glucose in water If there is excessive vomiting or diarrhea or intestinal ileus, the route is via the vena cava

TECHNIC — A no 9 F nylon catheter of the type used for cardiac catheterization is inserted into the right femoral vein via a cutdown on the upper end of the saphena magna vein Then the catheter is advanced into the inferior vena cava until the tip lies above the renal veins The cutdown wound is closed and an occlusive dressing applied The excess catheter protruding from the wound is then strapped to the limb allowing the patient to move freely in bed

There has been no significant clotting in the veins even after many days of continuous 50% glucose Fluid must flow continuously through the catheter lumen to prevent back flow into the catheter and resulting clot Heparin is added in a dose of 1 000 I U/500 ml fluid Despite this compact white thrombi tend to form around the outside of the catheter near the tip and a clot tends to form where the catheter is in contact with the vein wall There have been no pulmonary emboli no trouble when the catheter has been withdrawn and no wound sepsis at the point of catheter insertion

**Treatment of Renal Failure with Disposable Artificial Kidney Results in 52 Patients** are appraised by Shigeto Aoyama and Willem J Kolff[9] (Cleveland Clinic) Artificial kidneys remove retention products from the blood and correct imbalance of the plasma electrolytes through dialysis The small molecules of urea creatinine uric acid and other retention products diffuse from the blood through a cellulose membrane into the rinsing fluid At the same time the

(8) Brit. J S rg 45 160-164 Sept mber 1957
(9) Am J M d 3 565-578 Oct be 1957

electrolytes in the blood come into equilibrium with those in the rinsing fluid The advantages of the disposable coil kidney over other artificial kidneys are that it is prefabricated already sterilized convenient to set up and easy to operate

Ninety dialyses were performed in the 52 patients Of 29 with acute renal failure 15 recovered Of 23 with chronic renal failure 13 improved During or after dialysis symptoms of uremia—twitching convulsions disturbances in the sensorium vomiting and Kussmaul respiration—improved Changes in blood pressure during dialysis could not always be avoided Decreases in blood pressure if they occurred were controlled by transfusion of small amounts of blood Increases in blood pressure sometimes required administration of a ganglion blocking agent In 5 of 6 patients with intractable hypotension before dialysis the increase in arterial pressure during dialysis was beneficial and could be maintained

Hemorrhages due to heparin caused no serious problems (Nasal administration of oxygen and manipulation of other tubes through the nose should be avoided ) Electrolytes were corrected in a manner that could be predetermined by the composition of the rinsing fluid standardized rinsing fluids proved satisfactory

Urea clearance rates were determined during 11 dialyses at flow rates of 200 ml /minute The average clearance of 105 ml /minute was lower than that found experimentally Larger blood flows up to 540 ml /minute were used with an increase in clearance After dialysis a decrease of urinary output was insignificant in patients with acute uremia but pronounced in some with chronic uremia

The rate of ultrafiltration with the coil kidney approximates 300 ml /hour dialysis but it can be increased to 700 ml Ultrafiltration is advantageous as most patients with uremia are edematous

A patient with severe trauma crushing injury fulminant infection or intoxication should be given the benefit of dialysis before chemical changes in the blood indicate impending danger Such a patient may have to be dialyzed every 2 or 3 days

# The Digestive System

FRANZ J INGELFINGER, M D

# PART V

# THE DIGESTIVE SYSTEM

## ALIMENTARY TRACT

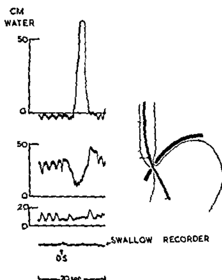
**Comparison of Cardiac and Pyloric Sphincters Manometric Study** The relation between structure and function at the esophagogastric junction and at the pylorus presents an interesting paradox A physiologic sphincter closing off the esophagus from the stomach has been postulated yet no anatomic sphincter has ever been convincingly demonstrated The pyloric sphincter on the other hand is a well-defined anatomic structure but it is doubtful that it functions as a physiologic sphincter

By measuring intraluminal pressures M Atkinson D A W Edwards A J Honour and E N Rowlands[1] (Univ College Hosp London) found a 1-4 cm segment of high pressure interposed between esophagus and stomach The upper limit of this segment was usually 2 cm above the diaphragm and its lower limit at the level of the diaphragm or 1 cm lower During a swallow pressure in this segment fell to general intraesophageal levels indicating that the high pressure segment represents a sphincter tonically contracted in the basal state and relaxing on swallowing (Fig 76) This sphincter was consistently demonstrated in 18 normal persons and in patients without evidence of hiatus hernia or free gastroesophageal reflux The high pressure segment cannot be explained by a flap or funnel valve nor can it be ascribed to diaphragmatic action An intrinsic sphincter must be postulated despite the absence of an anatomic sphincter

When intraluminal pressures were measured to determine whether a similar sphincter mechanism exists at the pylorus difficulties were encountered The fine open tipped

(1) La cet 2 918 922 N 9 1957

and air filled polyethylene tubes used to record pressure be came blocked by mucus or food particles and were hard to position at a particular point and fluoroscopic identifica ion of the site of the pylorus was not easy Therefore a chain of 4 overlapping balloons tied alternatingly onto 2 double channel polyethylene tubes was used By this means pres sures could be recorded with certainty at all points across




F g 76 —S multaneou t a ings fr n 3 pen-e ded t b w th rec rding t ps esophagu n egm nt of h ghe p e s e a d t ma h Dur g a w llow (DS dry swallow) p e su e falls i egm nt of h ghe p ess re befo e pe i talt c w e appears n ph ge l tr c ng (Court y f Atkin n M *et al* Lan et 9 8 9 Nov 9 1957 )

the pylorus without localizing the anatomic pylorus radio logically for the chain of balloons was long enough that some part of it must have been within the so called pyloric sphincter during withdrawal of the tube from the duodenum into the body of the stomach

An open ended tube wa withdrawn from the duodenum into the stomach in short steps 29 times in 18 normal fasting persons The balloon covered tube was similarly withdrawn 40 times in 7 persons and 23 times in 6 of these when food was present In contrast with results in the esophagus no band of increased pressure could be demonstrated in the re gion of the duodenal cap pyloric canal or pyloric antrum

(Fig 77) Phasic pressure waves were occasionally recorded simultaneously from the 4 balloons in the pyloric region presumably caused by partial or complete obliteration of the lumen but this closure was intermittent and brief and occurred as part of a contraction which periodically involved the whole pyloric region No independent sustained con

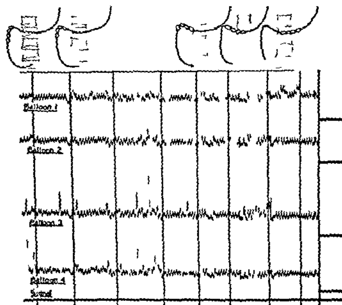



Fig 77 —T ac g f p as h n f balloon w thdrawn t p f m d o den m t tomach n n mal pe son B lloon mbe d 1-4 f om p ximal to di tal V rt al lines d t wh ecordi g wa t pped wh l t be w withd w t posi t on d cated n ppe most eg t N balloo h wa ta ed rise f p es as t p se th ough pyl r eg n (Courtesy f Atk son, M t ) Lan et 2 918-922 Nov 9 1937 )

traction from one part of the pyloric channel alone was recorded The pylorus apparently does not act antagonistically to peristaltic or other phasic pressure ranges by shutting down and remaining closed during successive contractions of the antrum

Except for intermittent systolic contractions involving the entire antral duodenal junction the pylorus unlike the cardia is normally relaxed contrary to the impression usually obtained clinically by x ray and studies of the anatomy

The concept of spasm of the pylorus presumably derives from the belief that a physiologic sphincter exists at the pylorus There is little support for this view It is premature to deny the occurrence of pylorospasm but there is some evidence that the concept has been grossly overworked as an explanation for a variety of symptoms in ulcer and nonulcer dyspepsia

► [This report raised some radiologic hackles and Dr A S Johnstone, the eminent British radiologist was impelled to write a letter to the editor (Lancet 2 1122 Nov 30 1957)

Sir I feel sure radiologists must have received a severe shock when they realized how many hours and countless ergs they had wasted trying to push barium through the pylorus which according to Dr Atkinson and his colleagues does not exist as a tonically contracted sphincter If it does not, what is that resists the bolus of barium which we so skillfully manipulate against the pyloric ring? Why is it so difficult to manipulate barium from the filled duodenal cap backwards into the stomach?

The answer to this question may be framed in another one what makes Dr Johnstone and his erg wasting colleagues believe that by pushing on the belly over the general area of the stomach they can differentially raise intragastric pressures over intraduodenal pressures to a sufficient degree to produce gastric evacuation? As a matter of fact, they probably can t at least in many individuals Pressure in the epigastric area even if applied over the gastric lumen is transmitted throughout the peritoneal cavity to viscera adjoining the stomach This is stated not merely on the basis of physical principles but also on the basis of direct observation. By using the very pressure recording devices that bother Dr Johnstone we can show that pressure applied to the upper abdominal wall over the stomach in a standing subject raises intragastric and intraduodenal pressure almost equally or intragastric pressure is increased over intraduodenal to such a slight extent that failure of gastric evacuation under such circumstances could in no way be interpreted as evidence of pylorospasm

Nevertheless the conclusions reached by Dr Atkinson and his colleagues are startling perhaps we must give up cherished concepts concerning gastrointestinal sphincters or perhaps technics used so extensively in the study of alimentary tract motility in man have serious flaws

In conclusion amen to the idea that pylorospasm is a grossly over worked diagnosis —Ed ]

**Studies in Achalasia of Cardia** Below the dilated body the esophagus in achalasia narrows down to a point This segment is easily seen at surgery and its muscular walls are normal in contrast with the hypertrophied and dilated esophagus above On postmortem examination it is not clearly seen because of the longitudinal contraction of this portion of the esophagus J R Trounce D C Deuchar R Kauntze and G A Thomas[2] (Guy s Hosp London) examined this area pharmacologically biochemically and histologically in patients with and without achalasia During Heller s operation longitudinal strips of muscle were

(2) Quart J Med. 26 433 443 October 1957

removed from the lower end of the esophagus in 7 patients with achalasia and compared with distal esophageal muscle resected in 5 patients for other reasons

Normal muscle contracted with acetylcholine and this contraction was increased by physostigmine Nicotine alone caused no contraction but after physostigmine was added four fifths of the samples responded and this response could be blocked by hexamethonium Response to both acetylcholine and nicotine could be blocked by atropine In patients with achalasia the strips responded to acetylcholine the response being increased by physostigmine and blocked by atropine but not by succinylcholine Five of 6 samples responded to nicotine after physostigmine

The findings suggest that normal muscle from the lower esophagus behaves like intestinal smooth muscle responding to acetylcholine but the response is blocked by atropine Enhancement by physostigmine suggests a cholinesterase mechanism The response to nicotine blocked by hexamethonium and atropine suggests the presence of active ganglion cells operating via cholinergic nerve endings The findings in achalasia of the cardia are substantially the same The response to nicotine after physostigmine which could be blocked by hexamethonium indicates presence of active ganglion cells within the wall of the esophagus and the response did not differ from that found in normal muscle

The muscle from the body of the esophagus in achalasia has been shown to have increased sensitivity to acetyl β methylcholine regarded as an example of Cannon s law However it may be due to diminished or absent cholinesterase in the esophageal wall in turn due to degeneration of the peripheral ganglion cells of the vagus with subsequent denervation of the esophagus When cholinesterase activity was measured manometrically on minced esophageal muscle no obvious differences were noted between normal and achalasic muscle Histologic examination showed normal ganglion cells in 2 specimens (Fig 78) in only 1 specimen were no ganglion cells seen

Thus in patients with moderately severe and advanced achalasia of the cardia the evidence indicated that active ganglion cells were present in the narrowed segment at the lower end of the esophagus This is contrary to previous opinions that failure of the cardia to relax is necessarily due

to degeneration of ganglion cells in that region removing the inhibitory effect of the vagus

That active ganglion cells were found in the lower segment of the esophagus in all but 2 patients with achalasia was surprising Probably ganglion cell degeneration in certain cases is confined to the dilated portion of the esophagus above the obstruction Previous studies may have missed this small lower section which becomes inconspicuous after death

Factors governing relaxation of the lower end of the esophagus are not fully understood Perhaps if the function



F g 8—D t l f g gl ll f m ph g f p t t w th h l f ca d a (C tesy of T e J R *et al* Q art. J Med 26 433 443 O t be 1957)

of the body of the esophagus is disordered the lower end might not receive the normal stimulus to relax Considerable evidence indicates that function in the main body of the esophagus is abnormal in achalasia and that normal peristaltic waves do not appear Histologic studies suggest diminution or absence of ganglion cells in the body During swallowing a co ordinated mechanism relaxes high pressure zones which are usually present at the top and lower end of the esophagus and allows passage of a normal peristaltic wave In achalasia this mechanism is disturbed peristaltic wave is absent and the lower zone does not relax If the function of the body of the esophagus were disturbed the whole co ordinated mechanism might be upset so that the lower zone *although otherwise normal* would not relax on swallowing

**Surgical Treatment of Cardiospasm (Achalasia of Esophagus) Considerations of Aspects of Esophagomyotomy** The aim of treatment is to weaken but not destroy the sphincter mechanism at the lower esophagus and cardia Success is variable after forceful dilation After one course of hydrostatic dilation 60% are permanently relieved another 20% enjoy relief after further courses

The Heller operation described in 1913 involves two myotomies of the distal esophagus and cardia one anteriorly and one posteriorly F Henry Ellis Jr Arthur M Olsen Colin B Holman and Charles F Code[3] (Mayo Clinic and Found ) did esophagomyotomy in 28 males and 27 females aged 4 76 with symptoms from 3 months to 44 years (average 10 years) Most had not responded to dilation Cardiospasm was mild in 7 moderate in 16 and severe in 32 Most patients had a huge elongated tortuous sigmoid shaped esophagus sometimes encroaching on the right pleural space

With achalasia of the esophagus normal peristalsis is absent in the entire esophagus Contractions may be noted after swallowing but not a co ordinated distally traveling peristaltic wave Surgery can relieve only the obstruction resulting from failure of relaxation of the lower esophageal sphincter No known procedure can restore normal motility The esophagogastric mechanism that prevents reflux must be preserved while part or all the mechanism that blocks passage from the esophagus to the stomach must be eliminated The vagus nerves must be identified and preserved for if they are injured pyloric obstruction may occur and reflux will be facilitated

TECHNIC —A long incision is made in the distal esophagus (Fig 79) deepened to free this portion completely from its encircling muscular fibers and the mucosa laid bare so that it protrudes through the incision At least half the mucous membrane of the distal esophagus is thoroughly freed The incision is extended generously upward over the dilated part of the esophagus and extended distally onto the stomach only far enough to divide completely all the distal esophageal musculature A long incision across the cardia leads to esophagitis and regurgitation and should be avoided The esophageal hiatus is not cut into or across The total length of the incision is usually 8-12 cm The patient is usually discharged 6 9 days after surgery

None of the 55 patients died in the hospital Of 45 patients operated on before Jan 1 1957 17 were followed by re

(3) J A M A 166 29 36 Jan 4 1958

examination and 28 by letter average follow up being 25 months Results were considered excellent if the patient was completely asymptomatic had gained weight and had returned to full time work good if he had gained weight and returned to work but occasionally had dysphagia when eating too rapidly or when nervous fair if improvement was definite but dysphagia persisted predominantly with solid

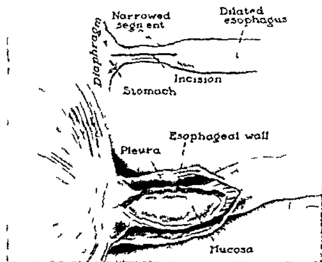



Fig 79—Esophagomyotomy—modified Heller procedure (Courtesy of Ellis, F H Jr et al J A M A 166 29 36 Jan 4 1958)

foods and poor if he was unimproved or if other symptoms had developed Results were excellent in 26 (58%) good in 12 (27%) fair in 5 (11%) and poor in 2 (4%) Certain types of food notably apples or raw vegetables may inconvenience patients with good results Benefit persisted in all but 2 in whom originally good results are now considered fair because slight dysphagia recurred 2½ years and 5½ years after operation

Objective studies in 35 patients up to 48 months after operation showed recognizable decrease in esophageal caliber in 17 In only 1 could slight regurgitation be produced by various maneuvers and he had an excellent result without symptoms of heartburn Some delay of passage from esophagus to stomach persisted in 13 of the 35 Neither of

these findings apparently had any direct correlation with symptomatic results

A zone of increased pressure in the lower esophagus is considered to represent the effect of a contracted lower esophageal sphincter Normally this relaxes on swallowing but not in cardiospasm Postoperatively the suprahiatal portion of this nonrelaxing zone of increased pressure was completely abolished but the subhiatal portion partially retained This remnant prevents esophageal reflux but the residual pressure is low enough to be overcome by the pressure of deglutition A gastric drainage procedure is not necessary Resting pressures in the body of the esophagus above the sphincter decrease after operation but the pattern of motility remains abnormal

Esophagomyotomy improved 96% and ended in good to excellent results in 85% of this series Regurgitation and esophagitis were prevented by not cutting muscle responsible for the subhiatal zone of increased pressure

► [It would be nice if a rational and successful surgical procedure for the relief of cardiospasm could be credited to discoveries made by basic physiologic studies Unfortunately Heller devised his myotomy long before Code and others delineated the normal function of the lower esophageal sphincter and its abnormal behavior in cardiospasm Nevertheless the various studies on the abnormal physiology of the esophagus in cardiospasm have made it clear that the surgical objectives in the treatment of this disorder are somewhat paradoxic resistance to aboral flow must be reduced without facilitating gastroesophageal reflux The too uccessful operation in the sense of achieving a wide ga troesophageal junction must therefore be avo ded. According to Ellis and his ollaborators this is accomplished by not extend ng the myotomy too far down on the gastric side of the junction thus apparently preserving some of the intrinsic sphincteric mechanism Thus although physiologic studies may not have led to the invention of the Heller myotomy they have at least contributed to its technic and definition

On the other hand surgery of any kind should rarely be necessary in cardiospasm because a properly executed forceful dilation of the narrowed segment is remarkably successful The dilating instrument a bag inflated under air or water pressure must of course be positioned accurately and this means positioning under fluoroscopic control not merely inserting the instrument for a certain distance beyond the incisor teeth In a pat ent with a huge and tortuous esophagus one or two days may be required to place the dilating bag athwart the gastroe ophageal junction

Dr Lamar Soutter has emphasized one other point

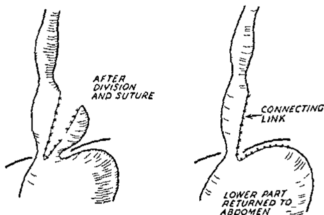
Average cost to patient of forceful dilation—$190

Average cost to patient of a Heller myotomy—$931 —Ed ]

**Operation for Hiatus Hernia with Short Esophagus** is reported by J Leigh Collis[4] (Birmingham England) Symptoms are usually severe in patients with a sliding type irre

(4) J Th ra S g 34 768 78 Dec mb 1957

ducible hiatus hernia an incompetent hiatus and a short esophagus In these cases the muscle of the right crus is weak or stretched the angle between the esophagus and stomach is opened out and reflux occurs On the other hand symptoms are often slight in those with a gastric lined esophagus In these normal crural muscle contracts with the rest of the diaphragm and maintains the acute angle between the esophagus and stomach during all phases of the respiratory




F g 80 (l ft) —Stoma h in ed b twe n cl mp P rt adj e t to l s r e rs s to f rm c ct ng tube p rt to p t nt left to be r t r ed t fu d
F g 81 ( ght) —C ect g tube only m ns abo d aph agm Late l p rt f tomach po ch r t rn d b low d aph gm ea e e of f ndus A ute a gle f im p ant t n of con ect g tube nt t m h has bee ht d
(Co rt y f Coll J l J Th r c c S rg 34 68 778 De embe 1937)

cycle This by itself controls reflux Children with so called gastric lined esophagus are asymptomatic demonstrating the efficacy of this control

The rationale of the operation devised is to control reflux by suturing the fibers of the right crus above and in front of the esophagus This lowers and makes more acute the junction of esophagus to stomach and is effective even if gastric tissue remains above the diaphragm

TECHNIC —The mediastinum is dissected to demonstrate the short esophagus and stomach pouch The gastric pouch is cleared of vascular attachments so that its surface is smooth and clean The supradiaphragmatic gastric pouch is then divided into 2 parts (Fig 80) One part essentially the area of the magenstrasse is left as a narrow supradiaphragmatic tube to connect esophagus and stomach The other to the left is returned below the diaphragm to enlarge the fundus A portion remains above the diaphragm as the connecting

tube (Fig 81) The limbs of the right crus are sutured together above and in front of the connecting tube

This operation was done in 9 women and 2 men One man aged 67 died postoperatively of coronary occlusion 9 patients recovered uneventfully Postoperative results were excellent in 7 Barium swallow 8 12 months after surgery revealed no reflux in 6 and slight in 1 Dysphagia was often marked after surgery and persisted for 3 weeks to several months

► [Although the results in this small series of cases are not overly impressive the procedure certainly looks ingenious on paper If it works in the future and in other hands it will do much to enhance the importance of the acute angle at the gastroesophageal junction sometimes known as the incisura cardiaca or the angle of His The role of this angle as a barrier to reflux appeals strongly to the mechanically minded but little positive physiologic evidence in its favor is at present available—Ed]

**Carcinoma of Esophagus Survival and Fallacy of Early Diagnosis** Almost all who write on this subject emphasize early diagnosis above all else and offer it as the solution of currently unsatisfactory surgical results Eddy D Palmer[5] (MC USA) observed 16 patients in whom the tumor was discovered before development of symptoms or first caused symptoms while the patient was under active medical surveillance for an unrelated disease These cases would represent the ideal early cases Four patients were asymptomatic and the tumors were unexpectedly discovered during roentgenologic or esophagoscopic examinations for study of cirrhosis pernicious anemia or cardiomegaly In the others the interval between the first clinical manifestation and detection of the tumor was no more than 9 days All patients had roentgenographic examinations Among the 15 who had esophagoscopy diagnosis was made grossly in 14

Seven patients including 3 of the 4 in whom carcinoma was discovered by chance during the asymptomatic period were considered inoperable when the lesion was detected Resection was possible in only 5 of the 9 operated on Three of the resected tumors involved the distal third of the esophagus and 2 the middle third Seven patients received deep radiation Peroral dilatations were used as indicated The course in general was short and 14 died of the esophageal carcinoma 2 died shortly after resection 4 survived a year and 2 were alive at the end of the 2d year

These patients offered the most favorable opportunities

(5) U S A m d F M J 8 1317 1322 S pt mb 1957

that can be attained with available diagnostic methods No one can doubt that early diagnosis is better than delayed diagnosis but it is clear that when the first symptoms appear most patients are beyond surgical care

Surgical resection should not be abandoned, regardless of its impotence as a cure because it furnishes two important palliative benefits (1) Whether or not removal of a primary tumor ever slows growth of metastases in esophageal carcinoma a large proportion of patients die of local effects of the primary tumor regardless of metastases (2) Esophageal occlusion is distressing and almost inevitable if prophylaxis is not undertaken Resection of high lying carcinomas is too hazardous to be justified for anything except intended cure but limited distal resection followed by peroral dilatations is often valuable in forestalling obstruction

The present rather unimaginative therapeutic approach to esophageal cancer warrants no more than mild interest until a better line of attack is found by means of serodiagnosis and chemotherapy

**Survey of Gastroscopic and Esophagoscopic Accidents Report of Committee on Accidents of American Gastroscopic Society** Results were compiled by Eddy D Palmer and C Wilmer Wirts[6] (Philadelphia) Two questionnaires 1 on gastroscopic and 1 on esophagoscopic accidents were sent to 890 doctors engaged in endoscopy in this country and to 40 in England Replies were received from one third The answers in 204 gastroscopy and 119 esophagoscopy questionnaires were suitable for compilation (table) About half the reporting esophagoscopists also reported on gastroscopy

Most of the gastroscopists and esophagoscopists had never encountered an accident but these were the physicians who had the smallest average experience After an endoscopist had carried out enough examinations the simple law of remote chance eventually exerted its influence The over all accident rate in gastroscopy was 0 079% and in esophagoscopy 0 25% The over all fatality rate in gastroscopy was 0 014% in esophagoscopy 0 059% Perforation was the main problem but anesthetic reaction also was important In 6 patients who bled the bleeding was not important Five patients died of acute myocardial infarction Symptoms in

(6) J A M A 164 012 015 A g 31 1957

these 5 occurred on the way to the gastroscopy room in 1 during preparation in 1 during examination in 2 and ½ hour after gastroscopy in 1

A total of 163 perforations occurred during gastroscopy resulting in 25 deaths Instrumentation was considered to have been easy in 117 instances difficult in 38 and unstated in 8 In the 25 patients who died instrumentation was considered easy in 20 difficult in 4 and unstated in 1 Perforation was recognized within 30 minutes of passage of the instrument in 81 patients and within ½ hour to 2 days in 78 The stomach was the commonest site of perforation Gastric perforation was moderately lethal and perforation of the distal esophagus most lethal The hypopharynx and adjacent proximal esophagus proved the most vulnerable although results of treatment were good In 2 patients the jejunum was perforated during postoperative examination of the stomach Of the 163 perforations 84 were managed by surgical drainage 68 medically and in 11 treatment was unstated Among the 84 patients drained surgically 16 died and 8 died among those treated medically only

GENERAL EXPERIENCES OF ENDOSCOPISTS

| | Gastroscopists | No of Gastroscopies Performed | Esophagoscopists | No of Esophagoscopies Performed |
|---|---|---|---|---|
| Totals | [illegible]04 | 267 17 | 119 | 40 540 |
| No accidents | 109 | 2 544 | 75 | 11,631 |
| Perforations | 81 | 1[illegible]2 044 | 4[illegible] | [illegible]6,6[illegible]9 |
| No accidents except from anesthetic | 10 | 13,[illegible]5[illegible] | 2 | [illegible]50 |
| No accidents except post examination bleeding and/or myocardial infarction | 4 | 9 032 | | |
| Total no who had experienced ethyl accident | 20 | | 5 | |
| Total no who had experienced post examination bleeding and/or myocardial infarction | 9 | | | |

During esophagoscopy 95 perforations resulted in 22 deaths The perforation was immediately recognized in 41 patients but not until after more than 30 minutes in 54 Most perforations were through the hypopharynx and upper esophagus The more distal perforations were the more dangerous In many the esophageal disease that led to the esophagoscopy appeared to be the direct explanation for the perforation Biopsy had been taken in 18 patients with perforation and 1 biopsy was proved to have caused the perfora

tion Medical treatment alone was instituted in 54 patients and surgical drainage in 37 Respectively there were 15 and 3 deaths

Forty two accidents were related to anesthesia 38 of which were due to a local anesthetic agent in the 10 patients who died the responsible agent was tetracaine (Pontocaine®) hydrochloride 2% in 5 tetracaine 1%, in 4 and cocaine 10% in 1 Four reactions were ascribed to other drugs used for pre examination preparation but these were of little consequence Information was not obtained on the technic used for inducing anesthesia (swab spray or gargle) or on whether epinephrine was routinely added to the anesthetic solution In 18 instances a barbiturate had been used for premedication in 10 it had not and for 10 no information was listed The main clinical manifestations during the reactions were convulsions cardiac arrest, cyanosis sudden shock and coma When death occurred it did so within a few minutes

► [Even though the questionnaire elicited the usual disappointing return (23% satisfactory replies on gastroscopy out of 890 questionnaires sent out) the results are most informative Note for example the incidence of accidents during procedures classified as easy by experienced endoscopists

The esophagoscopic accident rate of 0.25% (attempts to remove foreign bodies included) unfortunately does not give a breakdown between the experience of those using flexible and those using rigid instruments Many esophagoscopists using the traditional rigid instrument view the manipulation of the flexible scope with alarm It would be nice to know if this alarm is justified

Another vital question the analysists could not answer is related to the methods used when reactions occurred to topical anesthetics It has always seemed to me that sprays should never be permitted, for large amounts of a finely aerosolized anesthetic can be absorbed rapidly through the lungs —Ed ]

**Clinicopathologic Study of Large Benign Gastric Ulcers** John C Turner Jr Malcolm B Dockerty James T Priestley and Mandred W Comfort[7] (Mayo Clinic and Found ) in a search of the files between 1940 and 1954 found 100 chronic benign gastric ulcers which were 4 cm or over in diameter representing 4 1% of all cases of benign gastric ulcer treated surgically during this time Mean age of the 78 males and 22 females was 53 2 years (ranging from 3 months to 73 years) A symptom complex suggestive of peptic ulcer was present in 93 and 45 had had symptoms for 5 years or over the mean duration of symptoms being 6 years Gastric hemorrhage manifested as hematemesis oc

(7) S g Gynec & Ob t 104 746-750 J 1957

curred in 26 and vomiting was a significant symptom in 51

On the basis of x ray carcinoma was suspected in 40 and benign gastric ulcer was correctly diagnosed in 45 When the surgeon stated before resection whether the lesion was be nign or malignant erroneous diagnosis of cancer was made in 13 of 24 cases! Apparent achlorhydria after the Ewald meal was noted in 7 Hospital mortality was 7% In 95 pa tients the ulcers were located on or near the lesser curva ture and in 57 they involved the posterior wall In 3 it was located on the greater curvature In 66 the ulcer had per forated or penetrated Multiple gastric ulcers were present in 4 but in none were over 2 chronic gastric ulcers present Associated duodenal ulcers were found in 19

In the individual patient the large size of the ulcer does not necessarily signify that it is malignant Size is impor tant in deciding the management of a lesion Skin cardio vascular and tubercular diseases were not present to any significant extent Early surgical intervention is indicated because of the uncertainty of the clinical diagnosis danger of massive hematemesis and failure of defects of this size to heal on medical regimen The procedure of choice is excision of the lesion by subtotal gastric resection Diagnosis of ma lignancy should be established by frozen sections before ex tensive and radical resection is done That total gastrectomy was the operation performed in 3 of the 7 patients who died probably accounts in part for the mortality rate in these patients

**Some Notes on Pathogenesis of Duodenal Ulcer** are pre sented by J N Hunt[8] (Guy s Hosp Med School) Normal subjects and patients with gastric or duodenal ulcer secrete pepsin in amounts corresponding to the amount of acid se creted Patients with peptic ulcer secrete no more pepsin/ unit acid than do normal subjects when the stimuli are basal conditions histamine hypoglycemia or various forms of test meal Therefore the amounts or concentrations of acid can be measured rather than the concentrations of pepsin which are more tedious to determine

If gastric acidity were important in peptic ulcer any factor which increased acidity should cause or maintain an ulcer in the susceptible few Such a hypothesis explains some observations (1) Before puberty the mean acidity of gas

(8) Am J D g t D 2 445 453 S pt mb 1957

tric contents is the same in boys and girls and so is the incidence of peptic ulcer After puberty the mean acidity is greater in men and so is the incidence of duodenal ulcer (2) Acid concentration in gastric contents is greater in patients without duodenal ulcer than in those without ulcer basally and after food (3) The amount of acid secreted after histamine hypoglycemia, basal conditions and test meals is greater in men with duodenal ulcer than in those without Gastric secretion in women is increased during lactation and some peptic ulcers exacerbate during this period (4) Acidity and peptic activity of gastric contents are reduced during the middle trimester of pregnancy when ulcer symptoms may be diminished X irradiation decreases the secretion of acid by the stomach accompanied by healing of ulcers These facts are best explained by the hypothesis that the concentration of acid in gastric contents is one factor which determines the liability to peptic ulcer

Tissue resistance is also important Some patients with duodenal ulcer actually secrete less acid than normal persons even when the ulcer is active During hospital treatment the secretory response may remain unchanged though pain is alleviated and the ulcer heals Patients with active duodenal ulcers secrete no more than patients in remission An ulcer may occur during ACTH therapy without any evidence of change in acidity or peptic activity Rest in bed increases the rate of healing of gastric ulcers but is not known to reduce gastric secretion of acid

Hypersecretion by patients with duodenal ulcer might be the result of an increased peripheral secretory capacity and there is no need to postulate any abnormal secretory drive to account for basal hypersecretion of acid by these patients This concept is not in conflict with the reduction in hypersecretion after cutting the vagus nerves Vagus section also reduces the response to histamine by approximately the same percentage as it reduces the basal secretion of acid The vagi may exert some trophic action on the gastric mucosa maintaining its peripheral reactivity to all stimuli including histamine and the stimuli responsible for basal secretion

Receptors in the duodenum and small intestine inhibit gastric secretion in response to stimulation by fat and solutions of sugar and acid The inhibitory effect on gastric se

cretion reduced by intraduodenal glucose solution is the same however in normal subjects and those with duodenal ulcer A defect in the inhibitory mechanism is therefore not the major cause of hypersecretion in peptic ulcer patients Mechanical irritation produced by excessively rapid gastric evacuation also cannot be blamed for duodenal ulcers since tests do not substantiate the notion that patients with ulcers who have no clinical evidence of pyloric stenosis empty their stomachs unusually rapidly

**Milk Alkali Syndrome Hypercalcemia Alkalosis and Azotemia Following Calcium Carbonate and Milk Therapy of Peptic Ulcer** Symptoms usually begin within 3 8 days after therapy is begun with distaste for milk excessive dryness of the mouth and pharynx anorexia dizziness headache weakness or lethargy nausea and occasionally vomiting Conjunctivitis disorientation mental confusion psychotic reactions and stupor have been noted Julius Wenger Joseph B Kirsner and Walter L Palmer[9] (Univ of Chicago) in a review of 3 300 patients hospitalized with peptic ulcer from 1947 to 1956 found 35 in whom the syndrome developed Daily intake of calcium carbonate had not been precisely measured 2-4 Gm were prescribed 10 15 times daily and the daily intake was estimated as 20 50 Gm

In 18 patients the first indication was nausea The mean level of hypercalcemia when first determined on the 4th-6th day of symptoms was 14 7 mg /100 ml When calcium carbonate was stopped the serum calcium level fell to an average of 12 3 mg on the 12th day Four days after therapy was stopped the phosphorus level had decreased slightly to a mean of 3 2 mg /100 ml and it continued to decrease to a mean of 2 8 by the 16th day of symptoms Serum bicarbonate content averaged 38 2 mM /L

Azotemia ranged from mild in 1 or 2 patients to levels of 129 and 138 mg /100 ml in 2 others The mean value of blood urea nitrogen 57 9 mg /100 ml by the 10th day of symptoms had decreased to 46 1 mg and reached normal values by the 23rd day The urinary pH rarely was dependable as an index of alkalosis though the urine tended to be alkaline

Moderate hypertension was noted in 14 patients before development of the syndrome In 23 patients diastolic pres

(9) Gastroenterology 33 745 769 November 1957

sures exceeded 90 mm during the episode and the trend was toward moderate elevation of blood pressure during the height of azotemia In only a few patients did hypertension persist after hypercalcemia subsided Specific ophthalmologic examinations for calcium deposits in 15 patients revealed abnormalities in 6

Usually calcium carbonate was discontinued when diag nosis of hypercalcemia was established Additional therapy generally included intravenous fluids isotonic salt solution ammonium chloride and 5% dextrose in distilled water Seven patients received calcium carbonate for varying pe riods after recovery from the acute episode without recur rence of the syndrome and 4 continued the antacid during the episode without untoward effects recovering as rapidly as those in whom the antacid was discontinued

Of the 35 patients 16 had a definite history of pre existing hypertension and some of these had depressed renal func tion Chronic renal disease was present in 4 nephrolithiasis in 2 and benign prostatic hypertrophy in 2 Gastrointestinal hemorrhage also seemed to be an important contributory factor presumably because of decreased blood flow to the kidneys Eight patients had moderate gastrointestinal hem orrhage immediately preceding hypercalcemia Of the 35 patients only 1 showed the syndrome without obvious pre disposing cause and she had a past history of scarlet fever

Impaired renal function appears to be important in de velopment of the milk alkali syndrome whether the impair ment is due to pre existing hypertensive or renal disease dehydration alkalosis or gastrointestinal hemorrhage None of the patients showed evidence of hyperparathyroidism but this possibility has not been entirely excluded The ulti mate prognosis of the acute syndrome is favorable

► [Note that the patient does not have to take sodium salts to experience the milk alkali syndrome Furthermore not every ulcer patient with hyper calcemia has hyperparathyroidism

Are there no other ways of handling peptic ulcer than to give milk and antacids? Is it not crucial that the patient avoid fried foods that he give up smoking? Hasn t anybody found a new way yet of treating ulcer? See below —Ed.]

**Effect of Heated Fats on Gastric Motility and Acidity in Duodenal Ulcer** According to most standard ulcer diets fried foods should not be eaten and most patients with dys pepsia state they no longer eat fried foods even when not adhering to a definite diet In some patients this ma be due

to traditional advice but in many fried food does seem to cause or aggravate ulcer pain It is surprising that ulcer pain should result from fried food because fat inhibits gastric secretion and motility two of the main factors to which ulcer pain has been attributed

P H Friedlander and A Kerr Grant[1] (London) investigated whether fat heated or unheated stimulates gastric function or causes inhibition The studies were carried out on 46 patients with radiologically proved uncomplicated duodenal ulcer Partial gastrectomy later was done in 21 No evidence of pyloric stenosis was found Tubes were passed through the nose and placed under radiologic control so that the balloon was in the body of the stomach 40-60 ml air was injected into the balloon and pressure changes inscribed on a kymograph Recordings were made with the patient supine After 12 125 minutes fat was injected down the Levin tube To avoid any effect due to volume being misinterpreted as an effect caused by the fat itself an equal volume of water at 37 8 C was injected down the tube during the control period and a control solution of gum acacia in which the fat was in emulsion form was injected in 4 patients Pure beef and mutton fat were used unheated and heated at 200 250 C for varying times up to 42 hours A sample of mixed dripping also was tested The appropriate fat 20 ml at 37 8 C was injected down the tube

Twelve secretory studies were performed in 12 patients with radiologically proved uncomplicated duodenal ulcers In 4 diagnosis was subsequently confirmed when partial gastrectomy was done Initially the stomach was emptied as completely as possible but no attempt was made to prevent swallowing of saliva At 15 minute intervals samples of 5 10 ml gastric contents were withdrawn to obtain basal pH measurements The stomach was re emptied and 20 ml of the appropriate fat at 37 8 C injected into it Further samples of 5 10 ml were aspirated at 15 minute intervals for 2 hours Gastric motility was inhibited in 24 of the 32 patients in whom the stomach was active when the fat was injected In 5 there was no effect and in 3 the effect was doubtful When the fat was injected into the quiescent *stomach stimulation occurred in 4 patients and* there was no effect in 11 In only 2 of 15 patients in whom the stomach

(1) Cl S 16 731 741 N ember 1957

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gether 104 patients were included in the trials—80 smokers 24 nonsmokers

Size of the ulcer niche decreased by two thirds or more among slightly more patients who stopped smoking than among those who continued smoking (30 40 vs 23 40) Average reduction in the ulcer size in those who smoked less *but did not stop smoking was intermediate between these* two groups

Of 24 patients who were nonsmokers on admission in 14 (58%) the ulcer healed by two thirds or more average reduction in ulcer size was 61 3% These results were almost identical with those in patients who were not advised to modify their smoking habit The patients advised to stop smoking gained on average slightly more weight than those not so advised There is a strong clinical impression that weight gain is easier after smoking is stopped

Fewer of those advised to stop smoking were completely free from symptoms but the difference was not significant The proportion who had major symptoms i e daily pain for a week or longer was the same in both groups This may have been a chance finding independent of the treatment

The results are difficult to interpret Apparently smoking sometimes can be a factor in producing or maintaining a peptic ulcer That results were best in patients who stopped smoking completely is not in itself conclusive This might have occurred if the patients who stopped smoking were also more cooperative in other ways or if they were mentally more relaxed It is unlikely that smoking is an important direct cause of peptic ulcer Tobacco consumption particularly cigarets has increased in Britain over the past 2 3 decades whereas incidence of gastric ulcer probably has decreased In contrast incidence of duodenal ulcer has almost certainly increased but the association with smoking is less It seems more reasonable to suggest that smoking interferes with healing of the ulcer and thus helps maintain its chronicity

► [At a recent World Congress of Gastroenterology held in Washington D C in May 1958 experts from all over the world discussed the causes of peptic ulcer With understandable patriotism the Indian absolved spices the Frenchman wine and the Brazilian coffee Others made positive correlations and stated that ulcers reappeared with the seasons with the resumption of smoking with overeating *with undereating with making too* much money with having too little money and—naturally—with emotional stress Unfortunately in attempting to correlate ulcer recurrence with fac

was quiescent was there true stimulation There was no marked or constant change in tone No appreciable decrease in the group mean pH of the gastric contents occurred although individual experiments showed slight changes in either direction

The findings lend no support to the theory that fat or heated fat stimulates gastric motility or gastric acidity

► [It s like putting a needle into an overinflated balloon whenever some of the most venerable dietary beliefs are subjected to objective tests nothing much seems left after the pop Last year it was spices (1957 58 YEAR BOOK p 510) this year fats and orange juice which bothers so many ulcer patients has a pH considerably more alkaline than the pH of the ulcer patient s own gastric juice Specific foods seem to bother many people with dyspeptic symptoms but the mechanisms are certainly obscure —Ed ]

**Effect of Smoking on Production and Maintenance of Gastric and Duodenal Ulcers** was studied by R Doll F Avery Jones and F Pygott[2] (London) Comparison was made of the smoking habits of patients with and without peptic ulcer and the effect of advising patients to stop smoking was tested by controlled clinical trial Three groups were studied patients with gastric ulcer duodenal ulcer and those without ulcers Each ulcer patient was matched by 2 control patients of the same sex the same 5 year age group the same type of place of residence and the same socioeconomic group Data were available on *327* patients with gastric ulcers 338 with duodenal ulcers and 1 143 controls with diseases believed unrelated to smoking

For both sexes the proportion of nonsmokers was smaller in ulcer groups than in corresponding controls gastric ulcer men 1 3% vs 4 7% and women 31 1% vs 66 8% duodenal ulcer men 2 1% vs 5 8% and women 53 7% vs 62% In gastric ulcer the differences were statistically significant for both sexes but in duodenal ulcer they were significant only in men There was no consistent relation between the proportions of patients in the 3 groups and the amount of tobacco smoked In neither sex was there any significant difference between the age at which the duodenal ulcer patients and corresponding controls began smoking More men ulcer patients smoked cigarets than did their corresponding *controls*

Half of the patients in each ulcer group who smoked were advised to stop smoking the other half were given no advice Nonsmokers were advised to continue abstaining Alto

(2) Lancet 1 657 662 Mar 29 1958

sin in 2 patients showed a definite fall in excretion of pepsin at the peak of uropepsin elevation

► [The implication of these interesting findings would have been more persuasive if the results of more gastric pepsin determinations were available It is also not clear why the increased uropepsin value should not be ascribed to radiation induced damage of the chief cell Breakdown of chief cells is according to Hirschowitz (Physiol Rev 37 475 1957) one of the mechanisms believed to account for release of pepsinogen into the blood of persons with normal stomachs —Ed ]

**Glutamine in Treatment of Peptic Ulcer Preliminary Report** Raw cabbage juice was reported to contain a heat labile factor effective in treating peptic ulcer Another factor which reversed the toxicity of alcohol for certain microorganisms was found in cabbage juice and also is destroyed by heat This factor identified as glutamine has been isolated from cabbage juice Juices from different sources of cabbage vary in glutamine content and inability to duplicate the original results in treating peptic ulcer with cabbage juice may be due to variations in the amount of factor in the different cabbages

Glutamine contributes to the biosynthesis of the hexosamine moiety of certain mucoproteins It could stimulate mucin synthesis and thereby benefit peptic ulcer patients William Shive R N Snider Ben DuBilier Joe C Rude George E Clark Jr and Jerome O Ravel[4] (Austin Tex ) gave 400 mg glutamine in capsules 4 times/day 1 hour after meals and before retiring to patients with easily demonstrable ulcers i e an area 10 sq mm or larger by x ray The patients also received an antacid and antispasmodic and a bland diet No appreciable difference was noted in response of patients given glutamine from the outset and that of conventionally treated patients In most patients in both groups the ulcers healed in about 2 weeks

In 24 patients with gastric or duodenal ulcer treated with glutamine alone diet was not changed except that alcohol and highly seasoned and fried foods were avoided No other medication was given In half the patients the ulcers were healed at the first radiologic re examination at about 2 weeks and most patients were pain free in 1 3 days The ulcers healed in 22 of the 24 patients and only 2 required more than 1 month of treatment

In a further test 21 patients with peptic ulcer were given capsules containing glutamine or lactose Neither clinician

(4) T J Med 53 840 84 N mbe 1957

tor X the prevalence of factor X was determined only in those with recurrent ulcer symptoms for the most part no data were gathered as to how many asymptomatic ulcer patients had been exposed to factor X *without* suffering ulcer recurrence In contrast to such uncontrolled observations were the studies of England s Dr F Avery Jones of which the above is a nice example —Ed ]

**Effect of X ray Therapy on Gastric Acidity and on 17 Hydroxycorticoid and Uropepsin Excretion** was studied by J A Rider H C Moeller T L Althausen and G E Sheline[3] (Univ of California) in 13 men and 1 woman aged 40 73 Six had duodenal 5 gastric and 3 stomal ulcers Twelve received 1 475 1 700 r to the stomach within 12 days the other 2 were given 1 000 r within the same period All showed a decrease in gastric acidity after therapy Maximal fall of free hydrochloric acid occurred in 3 16 weeks Follow up tests 36 52 weeks later showed that gastric acidity had not returned to pretreatment levels in 4 of the 7 followed for this period in the other 3 decrease after therapy had never been impressive

Control uropepsin levels in the 14 patients ranged from 10 to 131 units/hour and rose significantly in each after treatment Average increase was about fivefold 1 8 weeks after therapy Subsequently values were almost identical with those noted before treatment The rise was much greater in patients in whom secretion of hydrochloric acid was markedly reduced

Urinary 17 hydroxycorticoid excretion rose in all subjects within 1 11 weeks after completion of therapy This excretion of 17 hydroxycorticoid is reminiscent of the response to general stress In most patients 17 hydroxycorticoid excretion returned to control or near control levels 6 52 weeks after treatment

Clinically the ulcer healed in 12 of the 14 regardless of its location In 1 the ulcer recurred but was much easier to manage medically

The findings may be explained by an alteration in function or permeability of the chief cells leading to a change in the direction of diffusion of pepsinogen in favor of the blood stream rather than actual destruction of these cells Serial biopsies show histologic changes which do not correlate well with the decrease in pepsin and acid secretions Simultaneous measurements of gastric pepsin and uropep

(3) An I t Med 47 651 665 O t be 1957

ach thus denervating it At this point Heidenhain pouch secretions increased by 47 3% over baseline values A fourth operative procedure reattached the antral pouch to the stomach wall to simulate its mechanical position before it was denervated Heidenhain pouch secretions following this procedure exceeded baseline values by 25 8% Finally at a fifth operation the antral pouch to the colon was completely excised and the colon defect closed Collections from the Heidenhain pouch thereupon decreased 57 6% below base line values

Mechanisms possibly responsible for these findings in clude (1) inadequate filling of the antrum during the in nervated phase and (2) neuronal ( vagal ) inhibition of the antrum which under the stimulation of mechanical disten tion is greater than any hormonal stimulatory influence Since the transplanted antrum appeared to be well filled by colonic contents before antral denervation the first explana tion appears unlikely The fact that denervation of the transplanted antral pouch profoundly stimulated Heiden hain pouch secretion may be taken as evidence favoring the existence of neuron inhibition of the antrum

► [An extensive literature is accumulating on the role of the gastric an trum in controlling gastric secretion For the most part experiments have been performed by creating Heidenhain pouches in dogs and then subject ing the antrum to various manipulations Since the Heidenhain pouch is an isolated pouch of stomach completely deprived of extrinsic innervation any change in its acid output following an antral manipulation should re flect the elaboration of an antral factor and its transmission to the Heiden hain pouch via the blood

Evidence at present is quite consistent that the antrum releases gastrin to stimulate Heidenhain pouch secretion when the antrum is distended or *exposed to food or chyme with a pH of 3 0 or above When the acidity of* food introduced into the antrum is greater i e pH less than 2 5 the Heidenhain pouch is not stimulated to secrete Some major questions re main however When the Heidenhain pouch fails to respond to the intro duction of acid foods into the antrum is this merely because gastrin release is not stimulated by acid foods or because such foods induce the release of an inhibitory substance counteracting the effect of gastrin? To what extent does the nervous control of the antrum influence its elaboration of gastrin? What is the site and the nature of antral elements that determine gastrin release?

Although results reported are far from uniform most evidence suggests that the immediate effects of antral stimulation depend on whether or not gastrin is released and that there is no need to postulate the existence of an inhibitory hormone directly counteracting the effects of gastrin. If for example two antral pouches are prepared in one dog and if Heiden hain pouch secretion is then stimulated by introducing a liver extract at *pH 7 0 into one of the two antral pouches the increased Heidenhain* pouch secretion is unaffected by introducing acid into the second antral pouch (Am J Physiol 191 64 1957) On the other hand acid profusion

radiologist nor patient knew which medication was being taken Fourteen received lactose and 7 glutamine Of the 14 on lactose 1 showed the ulcer healed at 2 weeks and 6 others at about 4 weeks In all 7 on glutamine the ulcers were healed at the second radiologic re examination—in about 4 weeks

Results of the study suggest that glutamine is probably more effective alone than the commonly used therapeutic regimen of diet antacid and antispasmodic in promoting healing of peptic ulcer

► [As material in recent YEAR BOOKS attests the search for new ways of treating peptic ulcer continues—new ways that are practical easy on the patient not alkalosis producing and effective in the long run Cheney's cabbage juice factor is here given a new lease on life albeit the role of glutamine is becoming all too prevalent in disorders pertaining to the abdomen it is recommended for hepatic coma it may have something to do with gluten sensitivity in patients with sprue and now it is advocated for the ulcer patient!—Ed ]

**Heidenhain Pouch Secretory Response to Transplantation of Innervated and Denervated Antral Pouch to Transverse Colon** Gastric acid secretion can be stimulated by the antrum and mechanical distention of a denervated antral pouch has been shown to produce a high incidence of peptic ulceration Vagal innervation of the pyloric antrum potentiates the excitatory action of liver homogenate mixtures on gastric secretion To elucidate the confused relation between the nervous and chemical control of the antrum Thomas W Jones John K Stevenson John E Jesseph Lloyd M Nyhus and Henry N Harkins[5] (Univ of Washington) determined the effect of denervation on the acid stimulating potentials of transplanted antral pouches In all experiments kennel temperature time of feeding and time of collection of pouch secretions were carefully controlled

The first operation consisted of the formation of a Heidenhain pouch and an antral pouch with intact innervation in dogs Thirty consecutive 24-hour Heidenhain pouch collections were made to obtain baseline values In the second operation the antral pouch was transplanted into the transverse colon but remained innervated because attachment of the antral pouch to the stomach was left intact along the lesser curvature Collections from the Heidenhain pouch revealed no changes from baseline values In the third operation the antrum was completely separated from the stom

(5) Ann Su g 147 13 16 Jan ry 1958

rior vena cava completely bypassing the liver and the lower inferior vena cava drained into the upper end of the portal vein maintaining a large flow of systemic venous blood to the liver

Each dog showed profound increase in mean acid output after portacaval transposition as both volume and acidity of the juice secreted by the pouch increased Two dogs died of perforating ulcers in the pouches The increased pouch secretion after transposition probably was not due to im paired parenchymal liver function Humoral substances re sponsible might be gastrin or ammonia but the exact agent responsible is unknown

► [This experiment which struck me as the neatest gastroenterologic idea of the year indicates that not only the gastric antrum determines the extent of the gastrin effect —Ed ]

Subtotal Gastrectomy and Hemigastrectomy with Vagotomy for Duodenal Ulcer Comparative Study One Year after Operation was made by Harold W Harrower Philip Cooper Reginald H Smithwick and Dorothy H Burke[7] at Providence R I Veterans Administration Hospital on 90 men Subtotal gastric resection performed on 45 included at least the distal two thirds and in many the distal three fourths of the stomach Hemigastrectomy and vagotomy (on 45) differed from subtotal gastrectomy only by lesser extent of re section and the addition of vagotomy All vagotomies were subdiaphragmatic All operations were elective the principal indications were intractability obstruction bleeding or a combination of these

Early surgical complications were somewhat more frequent after hemigastrectomy and vagotomy One patient in this group had a duodenal fistula from rupture of the duo denal stump Four of 7 instances of stomal dysfunction oc curred in the hemigastrectomy vagotomy group Stomal bleeding requiring transfusion occurred in 1 patient in each group Moderate diarrhea developed in 2 patients in the hemigastrectomy vagotomy group One patient with sub total resection had a wound infection Pulmonary complica tions (3 of them in the hemigastrectomy vagotomy group) included 4 instances of atelectasis and 1 of aspiration pneumonitis

The authors mortality for elective subtotal gastrectomy for duodenal ulcer has been about 1 5% *No deaths have oc*

(7) J A M A 165 1 70 1274 N 9 1957

of an isolated antrum may inhibit histamine stimulated secretion from a Heidenhain pouch (Am J Digest Dis 3 204 1958) Although evidence for an antral antigastrin effect is meager the possibility still exists that the antrum may under certain circumstances exert an inhibitory effect on gastric secretion

A number of investigators have insisted for some time that an intact intrinsic and extrinsic innervation of the antrum is prerequisite for normal gastrin release (A M A Arch Surg 75 552 1957) Consistent with this idea is the observation that exposure of the mucosa of the isolated antrum to solutions of atropine and of local anesthetics inhibits gastrin release from the antrum Studies show that gastrin release may be inhibited by local anesthetics without affecting antral blood flow or motility thus suggesting that the gastrin release mechanism is directly dependent on an intact cholinergic innervation (Am J Physiol 192 479 1958) The observations cited by Jones and his collaborators in the abstract above suggest that an intact innervation not only may potentiate gastrin release but also controls the secretion stimulating functions of the antrum under all conditions

To determine the site of gastrin release antral submucosal tissues have been sectioned and allowed to scarify (Surg Gynec & Obst 105 687 1957) and operations have been devised so that the effects of stimulating antral mucosa and musculature could be analyzed separately (A M A *Arch Surg 76 441 1958) Both these investigations indicate that antral* submucosal integrity is necessary for normal gastrin release in response to the usual stimuli and that nerve cells perhaps in Meissner s plexus may be the specific loci controlling the gastrin mechanism —Ed ]

**Increase in Heidenhain Pouch Secretion after Portacaval Transposition in the Dog** Several studies have indicated that peptic ulcers occur oftener in patients with cirrhosis of the liver than in those without cirrhosis Of 29 patients with portacaval shunts peptic ulcers appeared within 9 months after shunt in 2 with no history of ulcer In 4 patients reported by others peptic ulcers originated or underwent exacerbation after portacaval or splenorenal shunt

If the secretory hormone from the gastric antrum (gastrin) were inactivated in the liver and normally only a fraction of the gastrin originating in the antrum gets to the systemic circulation via the hepatic veins then if portal blood were shunted around the liver an increased amount of gastrin might gain access to the systemic venous circulation and stimulate the gastric parietal cells to secrete acid To test this hypothesis the effect of portacaval transposition on acid secretion from Heidenhain pouches was determined in 4 dogs by James S Clarke James C Hart and Robert S Ozeran[6] (Los Angeles)

The portal vein and inferior vena cava were transected and transposed and the cut ends reanastomosed end to end Thus portal blood drained into the upper end of the infe

(6) Proc Soc E per B l & M d 97 118 121 Ja y 1958

gastrectomy with vagotomy gives greater protection against recurrent ulceration than vagotomy with gastroenterostomy and fewer disabling sequelae than two thirds to four fifths gastric resection with vagotomy

► [Although the antrum appears to be so important in regulating gastric secretion removal of the antrum plus a great deal of the stomach itself does not necessarily insure against recurrent ulceration In one series of 240 duodenal ulcer patients treated by subtotal gastric resection the re currence rate of stomal ulceration was 9% (A M.A Arch. Surg 76 74 1958) If the other major mechanism controlling gastric secretion is elimi nated as well by combining vagectomy with distal gastric resection the *results should theoretically be better Perhaps they are for recurrent* ul ceration was observed neither by Harrower and his collaborators nor by Edwards *et al* who followed 294 patients with duodenal ulcer for 1 10 years after vagotomy and removal of the gastric antrum (Ann Surg 145 738 1957)

What are the clinical results of merely sectioning the vagi without re moving much of the stomach? Since an intact vagal innervation appears to play a role in the release of gastrin from the antrum vagectomy plus some sort of drainage procedure might suffice for the surgical therapy of duodenal ulcer A new approach along these lines is reported in the sub sequent abstract but its rationale may be questioned. Although the nature of the procedure prevents food from stimulating the antrum alkaline mate rial regurgitating from the duodenum presumably will bathe the antral mucosa and will cause some gastrin to be released despite the fact that the vagi have been cut Only two eventualities seem possible either the pro cedure of antral exclusion with vagotomy for the treatment of duodenal ulcer will fall by the wayside because of recurrent ulcerations (and I m betting on this in spite of the early good results) or all that work on the dog's antrum can be thrown in the wastebasket as far as man is concerned —Ed ]

**Antral Exclusion with Vagotomy for Duodenal Ulcer I Acid Secretory Studies on 50 Patients** are reported by William R Waddell and Marshall K Bartlett[8] (Boston) Mortality and morbidity after dissection of the duodenum and disagreeable sometimes disabling side effects after radical *gastrectomy necessary to forestall recurrence indicate need* of a new approach to surgical treatment of duodenal ulcer The rationale for antral exclusion and vagotomy is vagotomy minimizes or abolishes the cephalic phase of acid secretion and transection of the stomach and exclusion of the antrum allow no food to contact the antrum thus eliminating the gastric phase of acid secretion

The approach is through the abdomen The stomach is transected a proximal pouch of 50% of the stomach being left The distal portion is excised to about 6 cm from the *pylorus i e about half the antrum is excised The first loop* of jejunum below the ligament of Treitz is brought anterior to the colon and anastomosed to the gastric remnant

(8) A S g 146 3 11 J ly 1957

curred in over 100 patients subjected to hemigastrectomy and vagotomy

Evaluation of results 1 year after operation was based on subjective and objective criteria and a study of gastric secretions

Severe weight loss and dumping and moderate to severe disturbances of meal pattern were more frequent in patients who had subtotal gastrectomy whereas persistent mild to moderate diarrhea was more frequent in those treated by hemigastrectomy and vagotomy Two patients in the sub total gastrectomy group complained of recurrent ulcer symp toms and the diagnosis of stoma ulcer was confirmed radio logically Stoma ulceration was not detected in any patient after hemigastrectomy and vagotomy Thirty four patients in the subtotal gastrectomy group and 29 in the hemigastrec tomy vagotomy group were enthusiastic regarding surgical results and 9 and 16 respectively were satisfied The only 2 who were dissatisfied were those with stomal ulcers after subtotal gastrectomy

For functional studies gastric secretions were collected under basal conditions for 1 hour after peptone beef broth stimulation for 1 hour and after stimulation with intrave nous insulin for two separate 1 hour periods the lower of the two pH values being used There was little difference be tween the two groups of patients with regard to basal and broth specimens After insulin stimulation which produced the most free hydrochloric acid 40 (88 9%) in the hemigas trectomy vagotomy group and 30 (66 7%) in the subtotal gastrectomy group remained achlorhydric under all test con ditions Incomplete vagotomy in the hemigastrectomy group resulted in no greater production of free acid than that in patients who continued to produce free acid after subtotal gastrectomy

There was no apparent correlation between clinical find ings and results of gastric secretory studies except that 2 patients with gastrojejunal ulcers produced free hydrochlo ric acid in 1 of these the pH of gastric secretion was less than 3 5 under all conditions

As compared with subtotal gastrectomy hemigastrec tomy with vagotomy for duodenal ulcer has afforded better clinical results and a decidedly greater frequency of achlor hydria Reports of other investigators indicate that hemi

systemic effects as are observed in the dumping syndrome After gastric resection many patients have had plasma volume decreases without dumping symptoms These points suggest that other changes must be significant in producing the symptoms The frequent complaint of a sensation of warmth and heat during attacks suggested peripheral vasodilatation with shift of blood away from vital body centers as a significant factor

In the 15 patients plasma volume was determined by Evans blue dye and vasographic observations were made by the Winsor vasograph All showed a decrease in plasma volume ranging from 300 to 750 cc with maximum fall at the peak of the dumping symptoms The plasma volume decreases were consistently associated with a slight rise in the hematocrit Peripheral blood flow was increased in those who had moderate to severe clinical symptoms of dumping particularly in those who had dizziness weakness sweating and tachycardia These same patients also showed a definite increase in peripheral skin temperatures and in the amplitude of pulsations Those who had no increase or even decrease in skin temperature and peripheral blood flow had no weakness dizziness sweating tachycardia or sensations of warmth during induced dumping attacks Increases in peripheral flow when present ranged from 1½ to 12 times normal

Thus patients with severe clinical dumping have an abnormal response to sudden plasma volume reductions in that peripheral vasodilatation may occur instead of the protective and homeostatic vasoconstriction that would be expected The blood pressure remains stable despite peripheral vasodilatation This could be explained by opening of arteriovenous shunts rather than by dilation of the arterioles themselves or by compensatory vasoconstriction elsewhere

► [If the dumping syndrome expresses hypovolemia resulting when hypertonic food substances in the gut draw fluid into the intestinal lumen why do some patients after subtotal gastrectomy and gastrojejunostomy suffer from dumping whereas others do not? After all fluid shifts brought about by introducing hypertonic material into the small bowel must be a universal physiologic phenomenon This article offers a reasonable answer and suggests that those with a dumping syndrome are not necessarily the patients with subtotal gastrectomy who secrete most fluid into the gut after a meal rather they are patients unable to adjust normally to relatively moderate degrees of hypovolemia —Ed ]

**Nonsurgical Treatment of Perforated Peptic Ulcer** The classic way to control escape of fluid through a perforation is

All patients had active duodenal ulcers immediately before surgery Antral exclusion and vagotomy greatly depressed the secretion of acid After 6 12 months the average pH basal was 4 9 mean 4 1 minimum after broth 5 3 mean 4 7 minimum after histamine 4 1 mean 3 2 minimum and after insulin 4 5 mean 3 8 minimum The average volume/hour in the basal period was reduced to 81 ml compared with 96 ml preoperatively Among the 50 patients no acid was secreted postoperatively by 60% during the two basal periods by 74% after broth by 40% after histamine and by 52% after insulin hypoglycemia In 40% no free acid was noted in any of the 30 samples collected basally after broth after histamine and after insulin

Antral exclusion with vagotomy probably insures against recurrent ulceration and is probably more effective than vagotomy with posterior gastroenterostomy Subtotal gastrectomy or hemigastrectomy with vagotomy depresses acid secretion more than antral exclusion and vagotomy but the differences are small and require longer follow up and comparison of more patients to determine their clinical significance

Of 81 followed 6 months or longer 3 said that they were improved but were not entirely satisfied with the operation 6 have mild dumping syndrome controlled by reduction of the liquid volume and carbohydrate content of meals 4 have diarrhea and 1 had perforation of the duodenum 3 months postoperatively Anastomotic ulcers did not develop

**Peripheral Blood Flow and Blood Volume Studies in Dumping Syndrome** David B Hinshaw Eugene J Joergenson Harry A Davis and Clarence E Stafford[9] (College of Med Evangelists) studied 15 patients who had previous subtotal gastric resection most of whom had clinical manifestations of the dumping syndrome sensations of fulness or churning in the epigastrium associated with or followed by sweating tachycardia weakness syncope often a feeling of warmth occasionally explosive diarrhea and relief obtained by lying down Decreases in plasma volume that accompany the dumping attacks usually range from 300 to 750 cc The usual homeostatic mechanisms should compensate for this amount of volume reduction without such severe symptoms Other persons may lose 500 cc whole blood without such

(9) A M A A b S g 74 686-693 M y 1957

Essential to the success of the regimen are (1) patient co operation (2) proper position of the tube and (3) adequate gastric aspiration Because of excessive air swallowing improper placing of the tube or inadequate drainage air may fill the stomach leak into the peritoneum or both To control these developments x rays are taken on admission at 12 hours and before suction is discontinued Evidence of increasing pneumoperitoneum was found in 7 cases (3%) It can be treated by operation or by inserting a large stomach tube to insure better drainage

In 13 cases of perforation some other condition was diagnosed and at surgery the perforation was found and closed Seven cases of acute appendicitis and 2 of acute intestinal obstruction were treated as perforations for a period until the mistake in diagnosis was recognized and operations performed All patients recovered In 5 other cases (1 of acute enteritis 2 of coronary thrombosis and 2 of basal pleurisy secondary to bronchopneumonia) diagnosis of perforation was erroneous but obviously treatment which avoided laparotomy was correct Errors of diagnosis are probably evenly balanced between operators and aspirators Operators may make the sure diagnosis of an acute surgical condition but they occasionally open the abdomen of a patient who has an acute medical condition thus causing harm Aspirators may delay definitive therapy of an acute surgical condition

Of the 256 patients 21 treated surgically and 235 by aspiration 228 recovered The mortality was 11% Of the 28 who died 13 had operable disease and 15 were moribund when *first seen mostly old people with established peritonitis* profound toxemia and circulatory collapse who died within a few hours Only 9 deaths were attributable to the perforation or its complications and in none of these could the course of events have been improved by an operation to close the perforation

Gastric ulcer perforations and perforations in women carry special dangers The mortality rate of gastric ulcer (22 cases) was 25% Three of the 12 women died In six cases gastric cancer was present The incidence of malignancy was therefore 2 3% of all perforations and 21% of perforations in the stomach

*When classed into* acute and chronic ulcer groups on the basis of previous dyspepsia there were 79 patients with per

to suture it Hermon Taylor[1] (London) states the same results are obtained if the stomach is kept empty In either case closure of the perforation is by fibrin and fibrosis Fibrin is precipitated from the inflammatory exudate around the perforation and on the contiguous peritoneal surface so that the two stick together The main factor opposing this defense mechanism is continued or repeated flow through the perforation leading to infection and dissolution of the fibrin by bacterial toxins and leukocytes

Since 1944 the underlying therapeutic principle has been avoidance of operation unless indicated for some specific reason Patients in whom progress is doubtful are still operated on early and certain collections of peritoneal fluid are drained later Of 256 patients with perforations 21 had immediate surgery 27 intercurrent surgery and 208 were successfully treated by aspiration alone Twelve of the 256 were women

When the diagnosis of perforation is made ¼ gr morphine is given intravenously repeated in 10 minutes if necessary Prompt relief of pain gives the patient confidence in the hospital and encouragement to bear subsequent intubation which is carried out as soon as the morphine has fully taken effect The stomach tube is about ½ in in diameter and a suction bottle is applied to empty the stomach of large particles The large tube is then withdrawn and a nasoesophageal catheter is passed The stomach is aspirated by a nurse using an ordinary syringe removing and recording the amounts every 15 minutes then every half hour Mechanical pumps are not reliable An occasional small drink is permissible if it and the swallowed air are immediately withdrawn In an uncomplicated case treated early antibiotics are unnecessary The amounts of fluid and salt withdrawn plus the patient s requirements are replaced intravenously

After 24 36 hours if all goes well the perforation will be sealed and the patient may sip an ounce of water after each aspiration now done every hour The catheter should not be removed if any abdominal distention persists Suction is continued until peristalsis has returned After the tube has been removed the patient is given a gradually increasing diet and treated as if there were an acute exacerbation of the ulcer without perforation

(1) Gastroenterology 33 353 368 September 1957

hypoproteinemia usually found is not clearly associated with such symptoms as the patients may have i e intermittent epigastric pain anorexia vomiting and weight loss

Woman 37 had a long history of allergies She had clubbing of the fingers, recurrent dependent edema and marked hypoproteinemia of 2 8-3 6 Gm./100 ml of which 50 75% was albumin Roentgen studies suggested the diagnosis of giant hypertrophy of the gastric rugae which was confirmed by gastroscopy Repeated urinalyses were negative for albumin The icteric index was normal and no bromsulfalein was retained Thymol turbidity was 1 unit cephalin flocculation was a trace at 48 hours prothrombin activity was 100% erum cholesterol was 306 mg /100 ml and L E preparations were negative

The volume of gastric juice in 23 hours was 2,060 ml with pH of 5.8 No free gastric acid was obtained on 3 occasions but after alcohol caffeine stimulation the gastric juice contained 20 clinical units of free acid and 24 of total acid Nitrogen content of gastric juice was 84 5 and 87 3 mg /100 ml on 2 occasions and chloride 91 mEq /L

The patient died of acute myocardial infarction Autopsy revealed the stomach to be greatly thickened with boggy irregular consistency the serosal surface was smooth gray and glistening the mucosal surface showed pronounced hypertrophy of the rugae *Microscopically there were many dilated and cystic acinar structures lined* with mucus producing epithelium of a type commonly noted on the mucosal surface or in the neck of gastric glands of the normal stomach Gastric glands were relatively reduced The lamina propria was infiltrated with plasma cells and eosinophils The rugal stalks showed increased vascularity varying degrees of edema and some increase in connective tissue

This patient and 2 normal controls were studied After 1 day or more of iodine prefeeding each received 100 μc of $I^{131}$ labeled albumin in 20 mg carrier albumin intravenously The patient had extremely accelerated turnover as compared with the normal controls and the albumin pool was less than half that of the normal Thus she had a small pool turning over with great rapidity The gastric juice of the patient contained appreciable protein bound radioactivity estimated to represent 8 Gm albumin daily Electrophoretic analysis of the gastric contents revealed that the juice contained large amounts of serum albumin This was an unusual finding and corroborated the inference that large amounts of serum albumin were passed into the gastric juices by this patient The nitrogen content of the patient s stool was 1 8 Gm daily a high normal figure Stool radio activity was small representing less than 0.2 Gm albumin/day an insignificant amount compared to the daily turnover of gastric juice albumin

forations in acute ulcer and only 2 deaths in contrast to 26 deaths among the 177 cases of perforation in chronic ulcer a mortality of 15% The mortality rate of the perforation of an acute ulcer is thus low when the lesion is treated by aspiration Follow up studies showed that 13% of those with acute ulcer had recurrence whereas 85% of those with chronic ulcers had recurrence When surgical closure was done in another series 40% of patients who had acute ulcer perforation had subsequent relapses If the ulcer is already chronic and scarred it makes little difference in terms of relapse rate whether a perforation is treated by aspiration or by suture Acute ulcers however which will generally heal without a trace if treated nonsurgically are readily turned into chronic ulcers by inserting stitches into them

If a patient has general peritonitis and toxemia operation to remove the toxic fluid and close the perforation by an omentum graft should be done If the patient has an unrelated disease but also has a perforation aspiration of the stomach is indicated If the patient is not ill and has been without previous dyspepsia treatment should be by aspiration If previous dyspepsia has been present immediate partial gastrectomy will probably give the best chance of immediate recovery without further trouble There is no place for the simple suture of uncomplicated perforated ulcers The modern choice lies between the nonsurgical method of aspiration and immediate partial gastrectomy

► [Although the total mortality of 11% is in part explained by patients moribund on admission by avoidable errors in management and by intercurrent lethal complications it is this figure which must be compared with the total mortality of traditional operative treatment of perforated ulcer In recent years this has tended to drop below 10% and in one Veterans Hospital 93 consecutive male patients with perforated peptic ulcer were treated by the surgical method without any deaths (A M A Arch Surg 75 843 1957)

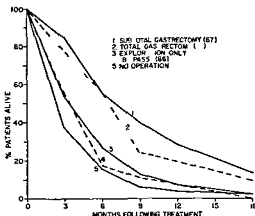
Dr Taylor's study shows that the nonoperative method of therapy is feasible that it is perhaps the method of choice in certain cases and that its success depends on adequate suction which must be scrupulously supervised.—Ed.]

**Mechanism of Hypoproteinemia Associated with Giant Hypertrophy of Gastric Mucosa** A case is reported by Yale Citrin Kenneth Sterling and James A Halsted (State Univ of New York) In 23 cases reported in the literature 16 patients had hypoproteinemia with levels below 6 Gm/100 ml and normal ratios of albumin to globulin The mild

(2) New England J Med 257 906-912 N 7 1957

longed life (Fig 82) The average survivals in postoperative months were 4 6 for exploratory laparotomy 4.2 for bypass 8 2 for noncurative total gastrectomy and 9 5 for noncurative subtotal gastrectomy

The most demanding problem in incurable gastric cancer is relief from obstruction pain bleeding and distressing digestive complaints Life may be an unappreciated burden to the patient with persistent pain or complete obstruction




F g 82 —D tion f lif for p tients w th cu ble c cinoma f tomach 1941 55 (Courtesy of Law ence, W J and M Nee G Cancer 11 8-32 Jan. Feb. 1958 )

Benefit from palliation depends on comfort and possible extension of life No patient obtained satisfactory relief from obstruction bleeding or other digestive complaints by bypass procedures Death may have been postponed but palliation was certainly not accomplished Gastrostomy and jejunostomy were equally unsuccessful patients with external feeding tubes being in general quite miserable Average duration of life after jejunostomy was 3 3 months after gastrostomy alone 6 9 months and after gastrostomy and radiation therapy 6 8 months Adjunctive radiation therapy led to some symptomatic relief occasionally but generally not

Of the 67 who survived palliative subtotal gastrectomy 57 were followed adequately Palliation was good in 31 6% fair in 24 6% and limited in 21 1% no relief was obtained in 22 8% Thus more than half of these patients had satisfactory

The radioactivity in the gastric juice represented almost half the patient s daily albumin degradation Since relatively insignificant amounts of radioactivity were recovered in the stool the albumin apparently was digested within the in testinal lumen and the amino acids reabsorbed Since the patient s fasting gastric juice contained markedly reduced amounts of pepsin mucoprotein and mucoprotease the gas tric juice nitrogen content was low normal and represented chiefly albumin

Although the albumin was not lost from the body as in nephrotic proteinuria the capacity of the body to synthesize albumin might be inadequate to compensate despite the availability of the constituent amino acids of the albumin in the intestine This is considered to be the probable patho genesis of the hypoalbuminemia and the reduced total pool of protein

► [Do you x ray the stomach in patients with hypoproteinemia of unknown origin?

In the case reported the explanation of the hypoproteinemia is ingenious but what conceivable metabolic defect would prevent the patient from assimilating the 8 Gm of albumin that apparently traveled the ga tro-enterohepatic circuit? Or what prevented her from making up the lo s by dietary means?—Ed ]

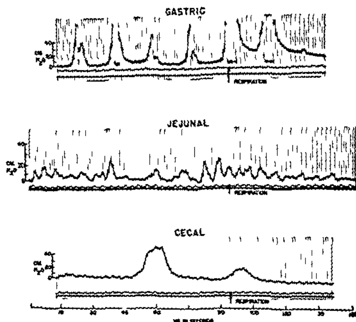
**Effectiveness of Surgery for Palliation of Incurable Gas tric Cancer** is reported by Walter Lawrence Jr and Gordon McNeer[3] Among 1 623 patients explored for gastric cancer at the Memorial Center for Cancer and Allied Diseases the disease was incurable in 47 1% because of liver or peritoneal metastases lymphatic spread beyond gross resection or in volvement of other organs not surgically resectable In about half the disease was too advanced for palliation but 379 had procedures intended to increase the duration and comfort of life Of the 379 141 (37 2%) had gastric resections and 238 (62 8%) bypass operations Operations were classified as palliative only if gross cancer remained at their completion

From 1931 to 1955 operative mortality for noncurative procedures was 7 8% for exploration only 16 8% for bypass 17 9% for subtotal gastrectomy and 27 7% for total gas trectomy On exclusion of patients with proximal subtotal gastrectomy postoperative mortality for distal subtotal re section was 11 4% Between 1931 and 1940 only 2 3% of pal liative operations were resectional but between 1951 and 1955 74 3% were of that type Resections definitely pro

(3) Can er 11 28 32 J n F b 195

of 0-100 c/sec The entire apparatus is calibrated in an external system before the capsule is swallowed Respirations are simultaneously recorded

The radio transmitter sends signals constantly until the battery charge is exhausted Therefore during 15 20 hours intraluminal pressure changes may be continuously displayed on a monitoring oscilloscope whenever the antenna




F g 83 Rec d of tr l mi l p u e f m th port m f ga t o nt tinal cr (C urt y f F J T t al 5 enc 126 9 5 9 6 \ 8 1957)

is near the subject Phasic pressure changes recorded as desired correspond in frequency and general appearance to the patterns recorded by other methods (Fig 83)

► {Sim lar instruments immediately dubbed gutnicks are being developed in at least ? other countries Although some major technical problems till have to be overcome one may anticipate that measurement of pH and of intestinal bsorption and excretion rates as well as intraluminal manometry will become feas ble by means of radio pills Doctor C F Code of the Mayo Cl nic even anticipates development of a device which may be swallowed before going to a cocktail party and which wi l emit siren like wails of warning should consumption of alcohol become exces s ve —Ed.}

palliation Of those with liver metastases only 33% had satisfactory palliation compared with 64% of those with peritoneal metastases average duration of life in both these groups was similar 7 2 and 7 5 months respectively The 7 patients with cancer that had extended to nonresectable organs showed the best results as 6 survived and had symptomatic relief for over 3 months

Palliative total gastrectomy resulted in longer postoperative survival than did bypass procedures but degree of palliation was less than in subtotal gastrectomy A difficult adjustment lasting 6 12 months usually follows curative total gastrectomy Most patients with noncurative total gastrectomy died before they could adapt to the physiologic changes of the operation and therefore were uncomfortable most of the time

In absence of distant metastases exploration should be done If incurable disease is found at surgery subtotal gastric resection should be done if feasible Total gastrectomy should probably not be done for incurable gastric cancer except to relieve obstruction

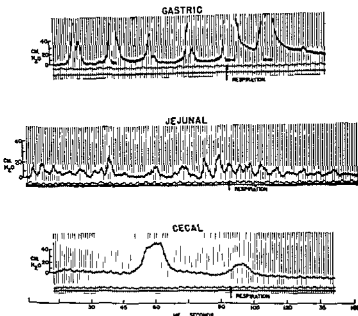
**Pressure-Sensitive Telemetering Capsule for Study of Gastrointestinal Motility** The prime objections to gastrostomy ileostomy colostomy or the passage of tubes into the intestinal tract to record pressures are (1) the distal small bowel and proximal colon are relatively inaccessible and (2) normal motility may be altered by the procedure

John T Farrar Vladimir K Zworykin and John Baum[4] (New York) devised an instrument sensitive to intraluminal pressures without connecting wires or tubes It is a rigid plastic cylindric capsule 3 cm long and 1 cm in diameter containing a transistor radio transmitter powered by a battery having a life of 15 hours A screw on cap at one end of the capsule permits replacement of the battery Pressure applied to a transducer at the other end of the capsule modulates the frequency of the oscillations generated by the transmitter An antenna secured loosely to the abdomen accepts the signals which are demodulated by a frequency modulation receiver and the pressure variations are recorded photographically Detected pressures range from 0 to approximately 50 cm water and the capsule responds to frequencies

(4) Sc 126 975 976 No 8 1957

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F g 83 —R l f t l m l p f m th port on f g t t t l t ct (C t y f F J T et l S 126 975 976 N 8 1957 )

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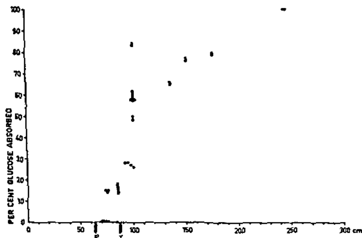
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(4) S e 126 975 976 N v 8 1957

distal small intestine The percentage of free fatty acids in the nonphospholipid fat at all intestinal levels is 65 70% These figures are higher than those earlier reported when animals and humans were fed nonemulsified fat in large quantities The finely emulsified fat used in the present study is probably more rapidly hydrolyzed Lipids recovered from the stomach 4 hours after a test meal generally contained




F g 84—Abso pt f f t gl c (pl l to ) d p ot d t d by I l gth of h m m ll t t e (C rt y of B g t m B t J J Cl I t 36 1521 1536 Oct be 1957 )

10 20% free fatty acids This may indicate activity of the so called gastric lipase or regurgitated pancreatic lipase

The concentration of glucose in the duodenum is usually never more than isotonic Hydrolysis of food protein is 10 15% in the stomach rapidly becomes 50-60% in the duodenum and thereafter remains rather constant The pH of the intestinal contents increases slowly from 6 0 in the duodenum to 8 0 in the lower ileum

The concentration of pancreatic enzymes over the length of the intestine varies widely and tends to decrease in the lower small bowel Apparently the enzymes are partly inactivated or autodigested in the enteric lumen but because the intestinal contents become progressively more concentrated the concentration of enzymes remains appreciable In the succus entericus invertase activity differs from pan

**Studies of Intestinal Digestion and Absorption in the Human** Through a polyvinyl tubing 2 1 mm in diameter B Borgstrom A Dahlqvist G Lundh and J Sjoval[5] (Univ of Lund) sampled different levels of the intestinal tract in 12 normal adult subjects with no known gastrointestinal disorder Polyethylene glycol which has a molecular weight of 3 000 3 700 was incorporated into the test meal a homogenized mixture of fat protein and carbohydrate with a distribution of calories of 40 15 and 45 Polyethylene glycol is highly soluble in water but is not absorbed or decomposed in the intestinal tract thus serving as a reference substance in measuring absorption Samples were taken from the duodenum or first part of the jejunum at 30 or 10-minute intervals Later and at lower levels hourly samples were taken In only 1 was sampling successful over 300 cm from the nose The sampling does not aim for complete recovery but the amount of test meal in each sample can be calculated from the concentration of the reference substance

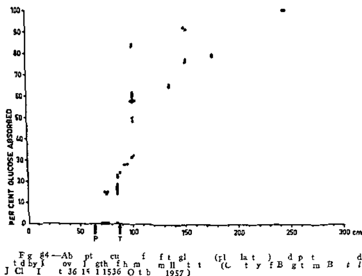
The general trend was a threefold to fivefold dilution of the test meal in the duodenum the 500 ml test meal increasing to 1 500 2 500 ml followed by concentration further down the small intestine Absorption begins in the distal duodenum and is generally completed in the first 50 100 cm of jejunum a little higher up for fat than for glucose (Fig 84) and protein In the lower small intestine the glucose concentration reaches zero At all levels there are some substances which are extractable with fat solvents This fat is mainly of dietary origin as proved by the recovery of $C^{14}$ triolein which was added to the test meal

The absorption of radioiodinated human serum albumin added to the test meal to differentiate food from endogenous protein did not exceed 80 90% even at the lowest levels of the small intestine Absorption of protein in the small intestine is thus less complete than that of glucose and fat As fecal excretion of radioiodine is low some protein must be broken down in the large intestine

The extent of absorption depends more on the location of sampling than on the time elapsed after *ingestion of the* test meal In man fat is absorbed over the entire length of the small intestine Experiments in dogs and rats had previously led to the conclusion that fat was absorbed only in the

(5) J Clin Invest 36 1521 1536 October 1957

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F g g4 —Ab pt cu f f t gl (gl la t ) d p t d t d by I ov l gth f h m m ll t t (C t y f B g t m B t l J Cl I t 36 15 1 1536 O t b 1957 )

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creatic enzyme activity In the duodenum and proximal jejunum where invertase activity is low pancreatic enzymes are maximal and disaccharide absorption efficient Perhaps disaccharide splitting enzymes in the succus entericus are not important for absorbing disaccharides

Phospholipids in the intestinal content after a test meal free from phospholipids are derived from bile lecithin The gallbladder empties during the first half hour after ingestion of a test meal During this time bile constituents are present in high concentrations in the upper small intestine The total amount of bile acids that passes into the duodenum used for digestion and absorption of the test meal is 4 8 Gm as a minimal figure Since the total circulating bile acids determined by isotope dilution is about 3 58 Gm the bile salts must be excreted into the intestine and reabsorbed about twice during digestion and absorption of a test meal Thus the triglycerides (30 Gm ) contained in the test meal are mixed in the intestine with about 20% of their weight of bile acids and 2 5 5% of lysolecithin a product of bile lecithin

► [The use of nonabsorbable materials as reference standards is finding increasing application to discover what happens in the enteric canal after a meal is eaten Some neat calculations are thereby possible to determine the intestinal concentrations of various exogenous and endogenous substances The technic however has its usual quota of intrinsic problems If particulate matter such as chromic oxide is used as reference standard the water soluble portions of a test meal may conceivably rush downstream ahead of the particulate matter and a relatively low concentration of a water soluble food in an aspirated sample will not necessarily mean absorption it may merely mean that the reference material has lagged behind the food On the other hand water soluble food in a pool of intestinal contents might be aspirated more easily than particulate matter lying at the bottom of the pool and thus the relatively high concentration of food with respect to the reference standard would reflect a technical artefact rather than a physiologic process

Polyethylene glycol used in the study here reported is water soluble but the question may be raised whether it is truly and completely unabsorbable It is believed to be not absorbed and not decomposed in the gastrointestinal tract on the basis of studies carried out principally in certain ruminants whether polyethylene glycol is similarly inert in the human gut requires further study Despite these reservations the results of the technic may be accepted as approximately correct and again demonstrate the fantastic rapidity of the absorptive process —Ed ]

**Intestinal Digestion and Absorption after Billroth II Gastrectomy Preliminary Report** on 5 patients is presented by Rene Kiekens and Goran Lundh[6] (Univ of Lund) In the past impaired digestion after gastric resection has been ascribed to rapid emptying of the stomach remnant acceler

(6) Act h ac d 113 349 356 1957

ated passage of food through the intestines decreased flow of bile and pancreatic secretion secondary to impaired stimulation and imperfect mixing of food with bile and pancreatic juice

METHOD—A narrow polyvinyl tube is passed through the entire intestine Holes 1 5 2 m apart allow collection of intestinal juice from 2 levels The fasting patient is given a 300 ml test meal i e 18 Gm fat 15 Gm protein and 45 Gm glucose $I^{131}$ labeled human serum albumin is included to label the food protein and separate it from endogenous protein A water soluble nonabsorbable and nondigestible substance polyethylene glycol is added to enable determination of the degree of absorption of fat protein and glucose Bile and trypsin concentration is determined spectrophotometrically In the upper jejunum samples are taken every 10 minutes during the first hour and then hourly

In normal patients the food concentration gradually rises to a maximum in 1 hour and remains constant in the duodenum for about 3 hours When food enters the duodenum the gallbladder empties and the concentration of bile is high even though diluted by the food Trypsin concentration also high at the beginning decreases through dilution by food and then is increased to 400 800 µg/ml by pancreatic secretion

After gastrectomy emptying into the jejunum is precipitate and food passes along the intestines in high concentration After 30 40 minutes the concentration of food in the upper jejunum is low and apparently most of it has left the stomach In the first half hour the concentration of bile and enzymes is low When the food has passed both bile and enzymes increase but enzyme levels never approach those found in normal subjects Bile concentration sometimes becomes quite high perhaps due to emptying of stagnated bile from the afferent loop In all the patients gastric emptying was not co ordinated with bile and pancreatic secretion Much of the food passed along the intestines rapidly with low bile and enzyme concentration

Protein absorption was only 10% and fat absorption 60% in the 1st hour when most of the food passed with little admixture of enzymes During the 2d 3d and 4th hours when the enzyme concentration rose absorption became almost normal but this affected only a small part of the test meal Total absorption of protein was 22% and of fat 80% In controls 60 70% of the protein and 85 90% of the fat is absorbed

at the same intestinal level Absorption of the protein closely follows the concentration of trypsin

The disturbed digestion and absorption following Billroth II gastric resections is due more to the low concentration of enzyme and imperfect mixing of food and enzymes than to rapid passage of food through the intestines Glucose ab sorption is almost complete but delayed and fat and protein absorption is decreased

► [This illustrates a neat application of the method outlined in the pre vious abstract and provides creditable evidence in favor of one of the theories proposed to explain such absorptive disturbances as occur after subtotal gastrectomy with gastrojejunal anastomosis —Ed ]

**Jejunal Biopsy after Partial Gastrectomy** is reported by I McLean Baird and O G Dodge (Univ of Sheffield) Iron deficiency anemia and steatorrhea are well recognized com plications of gastrectomy but their pathogenesis is unclear Iron and fat are absorbed through the mucosa of the small intestine Iron deficiency anemia is also often associated with gastric atrophy Results of biopsy of the mucosa of the ef ferent loop of jejunum in 32 patients after partial gas trectomy were compared with those of presumably normal jejunum in 11 patients taken at the time of subtotal gas strectomy Biopsy was unsuccessful in 3 of the 32 patients

METHOD —Bowden wire in an airtight plastic tube was guided un der radiologic control to the efferent loop of jejunum Suction was applied to the proximal end by a 20 ml syringe and rubber tubing The wire attached to a knife blade at the terminal was manipulated to pull up the blade thus cutting off the fragment of mucosa which had been sucked into the lateral hole of the tube The specimens were small disks of mucosa about 0 3 cm in diameter

In 23 of 31 specimens taken 3 months to 9 years after gas trectomy the jejunal mucosa appeared similar to that in the 11 taken at operation They were classed as normal and con tained normal numbers and distribution of mucus containing goblet cells Paneth cells and Kultschitzky cells In 4 some villi were thick and the stroma was edematous particularly at the free ends Mild atrophic changes were seen in 2 with the villi somewhat shorter and stubbier than normal One patient with postgastrectomy steatorrhea showed inflamma tory changes and the cellular content of the mucosal stroma was increased

Among 17 patients with postgastrectomy iron deficiency anemia jejunal mucosa biopsy was normal in 14 2 showed

(7) Qu rt J M d 26 393-400 J ly 1957

hyperemia and 1 jejunal atrophy Among 5 with postgas trectomy steatorrhea 3 biopsies were normal 1 showed atrophy and 1 jejunitis Although moderate steatorrhea may be present in some patients after gastrectomy inflammation or atrophy is not consistently seen The time interval be tween gastrectomy and subsequent biopsy did not affect in cidence of jejunal mucosal changes

► [This article deals a solid blow to those theories mostly speculative that various postgastrectomy complaints ranging from dumping syndromes to malabsorption and anemia are caused by chronic inflammatory changes of the jejunum near the stoma.—Ed.]

Duodenal and Jejunal Biopsies II Histology I Doniach and Margot Shiner[8] (Postgrad Med School London) per formed duodenal and jejunal biopsies on 45 patients In 25 of 30 patients with clinical diagnosis ranging from dyspep sia to peptic ulcer ulcerative colitis hiatus hernia chronic pancreatitis iron deficiency anemia and the posthepatitis syndrome duodenal biopsy showed normal mucosa The specimens measured 1 12 mm and usually contained the full mucosa a strip of muscularis mucosae and often submucosal connective tissue Mucosal dimensions and intensity of cell infiltration of the lamina propria varied markedly Mucosal thickness including villi varied from 150 to 350 μ The villi were 250 500 μ long and 75 250 μ thick Cell infiltration was less marked in the villi than between the glands of Lie berkuhn Nerve cells and fibers of Meissner s plexus were often prominent in the submucosa where lymphocytes were sparse and mast cells seen only occasionally The villi (Fig 85) showed well preserved epithelium in saw toothed ar rangement and a large number of lymphocytic nuclei were invariably present in vacuoles within the epithelium

Five of the 30 patients showed an abnormal duodenal mu cosa and submucosa Two showed striking deviations in 1 the villi were remarkably flattened and the other had chronic inflammatory exudate in the submucosa Three others showed gross distortion or atrophy of villi or glands in creased goblet cells abnormal epithelial cell nuclei or gross infiltration of the lamina propria with chronic inflammatory cells

Woman 61 had steatorrhea of undetermined origin with megaloblastic anemia due to folic acid deficiency Biopsy of the duodenum showed the mucosa to be 300 500 μ thick The villi were grossly blunted only 100 200 μ long and abnormally wide (50 300 μ) Vil

(8) Gast oe t logy 33 71 86 J ly 1957





F g 85 (t p) —\ gat dy p ps n m l d d l m d mal ll w th oc l b h g n w m g d 41 N t v l s cont g lymphocyt nucl n co r g ep th l l lay H m t ylin-e d ed f m ×175

F g 86 (b tt m) —Th k d ll nd d tend d ypts a d gl nd f L b k b H m toxyl -eo n d d f m ×130

(C rt y f D n h I nd Shin M G t nte l gy 33 71 86 July 195 )

lous surface area was markedly decreased The covering epithelium appeared normal The lower sides of the shortened villi formed the necks of gaping crypts of Lieberkuhn and were rich in goblet and argentaffin cells The glands were distended and rich in goblet cells Fig 86)

Jejunal biopsies in 9 of 15 patients showed full thickness mucosa muscularis mucosae and small amounts of submucosa The mucosa averaged 180 μ in thickness and the villi 470 μ in length The mucosal thickness did not vary much but the length of the villi varied considerably These sections differed from those in duodenal biopsies in elongation and thinning of villi more prominent and thicker striated border of surface epithelial cells and a more marked saw toothed pattern of the epithelium covering the villi Smooth muscle strands were more prominent in the jejunal villi The granules of the jejunal Paneth cells were a little larger than those *of the duodenum Abnormal jejunal mucosa was found in 6* patients 2 showing a striking loss of villi and 4 slight mucosal atrophy or increased cells in the lamina propria of the villi

The findings in duodenal biopsies do not support previous opinions that duodenitis may (1) be the basis of some dyspepsias (2) be associated with gastritis (3) precede duodenal ulcer or (4) be associated with peptic ulcer None of the 19 patients (8 of whom had proved gastric or duodenal ulcer) *with dyspepsia as a primary symptom showed histologic inflammation of the duodenum*

The duodenal biopsy of the patient with steatorrhea was strikingly similar to the jejunal biopsies of another patient with teatorrhea and the jejunal biopsy of one with megaloblastic anemia Most impressive was the almost total loss of villi Perhaps the malabsorption syndrome of these patients is in part due to the tremendous loss of villous surface epithelium

**Jejunal Biopsies in Sprue** During laparotomy for unrelated causes Charles E Butterworth Jr and Enrique Perez Santiago[9] (Hato Rey Puerto Rico) obtained jejunal biopsies 6-10 in from the ligament of Treitz in 0 patients with sprue and malabsorption and in 15 controls In 1 control diarrhea and severe megaloblastic anemia developed post partum but absorption tests were normal

Criteria for normal absorption are for xylose—a 5 hour

(9) A I t. M d 48 8 9 J ry 1958

urinary excretion of 4 4 Gm or more after an oral dose of 25 Gm of d(+) xylose for vitamin A—serum levels of at least 75 µg at 5 hours and 125 µg at 7 hours after an oral dose of 300 000 units for butter fat—serum optical density reading 0 1000 or more 2 3 or 4 hours after ingestion of a standard meal containing 30 Gm butter In addition 24 hour fecal fat



F g 87 —J j l b op y f m p t t w th p (C t y f B tt w th C E Jr d P S tiag E A Int M d 48 8 9 Janua y 1958)

was determined for 12 days in 4 of the 6 patients Normally the daily average fecal fat does not exceed 5 4 Gm under these conditions

The normal jejunal mucosa has slender delicately ruffled villi which project freely toward the lumen for over half the thickness of the mucosa In biopsies obtained from the patients with sprue the absorptive surface was considerably decreased the villi widened and adjacent villi apparently coalescent The free ends were shortened and the crypt portions thickened and more tortuous than normal (Fig 87) For comparable lengths of intestine the length of the columnar layer in cross section was 3 times as long in the control as in the untreated patient with sprue For identical squares of bowel the surface area of the control was 4 times greater than in the untreated patient

In each patient some inflammation but no marked thinning of the lamina propria was present No hyaline degen

eration of the villi was noted Microscopically each specimen showed edema In 4 of the 7 biopsies from patients with sprue the columnar epithelium showed increase in goblet cells This may account for the increase in small bowel mucus and the clumping of barium sulfate seen in x rays in such patients The columnar epithelium showed flattened cells marked vacuolation of the cytoplasm nuclear debris and paucity of nuclei The normal columnar layer with abundant cytoplasm and nuclei in palisades had been replaced by a thin shell of cell remnants Irregular dark staining nuclear fragments appeared to be remnants of leukocytes

The submucosa was normal in the untreated subject but showed slight to marked edema and congestion of vessels in the others Although starvation may cause intestinal atrophy none of the subjects was severely malnourished It is possible that some of the pathologic changes in jejunal biopsies from patients with sprue result from disturbances in the epithelial surfaces Diminished production or shortened survival of columnar cells could by jeopardizing the integrity of this surface lead to all the changes noted Intestinal involvement may be only part of a diffuse process which affects bone marrow and other tissues

► [The cases here reported may be regarded as cases of tropical sprue Similar changes of villous clubbing and flattening and of mucosal atrophy have been described by Dr Shiner and others in nontropical sprue Dr Cyrus Rubin of Seattle Washington has shown that the small bowel in the celiac syndrome of children is similarly affected There thus appears to be a common histologic denominator characterizing three syndromes that also present many clinical features in common. Are the histologic changes specific and are they intimately related to the faulty absorption of sprue? It is too early to answer this question Villous clubbing and mucosal atrophy may be found in a variety of chronic small intestinal diseases and in the interrelationship of malabsorption and small bowel pathology the cart and the horse cannot yet be clearly distinguished Soon it will be known whether the low gluten diet produces histologic as well as clinical improvement in celiac disease and sprue steroids apparently can benefit sprue without necessarily improving the appearance of the lining of the small bowel (J Mt Sinai Hosp New York 24 273 1957) —Ed ]

**Ulcerative Jejunitis in Polyarteritis** Abdominal pain has been reported in 57 70% of patients and other abdominal symptoms—anorexia distention nausea hematemesis diarrhea and jaundice—in as many as 76% of a series of patients with periarteritis nodosa Infarcts hemorrhages ulcerations and perforations of the intestinal wall have been found

in as many as 70% Alice Ettinger and Ruheri Perez Tamayo[1] (Tufts Univ ) report a case

Man 57 was hospitalized for nausea and diarrhea Six weeks be fore admission he had a rash on the dorsum of the hands and 2 weeks later migratory polyarthritis hematemesis abdominal cramps and bloody diarrhea The sputum was occasionally blood tinged A bari um enema was negative and a gastrointestinal series showed some irregularity of the descending duodenum He showed anemia gener alized purpura and acute renal insufficiency with oliguria and uremia On the 26th hospital day after severe epigastric pain and hemateme



F g 88—Ul t d j j m (C t y f Ett g r A and P T m y R R d l gy 68 669 672 M y 1957 )

sis a repeat gastrointestinal examination revealed 2 ulcerated some what narrow jejunal loops (Fig 88) similar to or identical with those een in acute regional enteritis On the 74th hospital day he died in shock with symptoms of an acute abdominal catastrophe

At autopsy acute generalized fibrinous peritonitis secondary to perforation of the jejunum was noted Just beyond the duodenum the jejunum was dark red with a thickened wall and a ragged heaped up mucosa which was perforated by a hole 0 4 cm in diameter sur rounded by multiple small but grossly visible ulcerations extending over about 1 ft of gut The excrescences were areas of surviving mucosa which had not sloughed The mucosa from stomach to sigmoid colon was riddled with small hemorrhages Pathologic diagnosis was allergic vasculitis involving intestinal tract lungs and kidneys with perforation of jejunum and peritonitis

► [A recurrent problem is the relation of granulomatous inflammatory disease of the small and large bowel to the collagen disorders regional

(1) R logy 68 669 672 M y 1957

ileitis has been regarded as a manifestation of sarcoid and some believe ulcerative colitis to be a collagen disease Yet radiologic evidence of small bowel involvement in such typical collagen disorders as disseminated lupus erythematosus and polyarteritis is not common—Ed ]

**Adenocarcinoma Occurring in Regional Jejunitis** Jejunal carcinoma is rare Peter Kornfeld Leon Ginzburg and David Adlersberg[2] (New York) report 2 instances of carcinoma occurring at the site of segmental stenosing granulomatous jejunitis and suggest that this represents a hitherto unrecognized complication of jejunitis

CASE 1—Woman 36 had gastrointestinal symptoms of severe diarrhea at age 28 when x ray studies revealed colitis Laparotomy revealed an inflamed large intestine At age 30 she was treated with Aureomycin® and small doses of cortisone with clinical improvement At age 34 x ray studies revealed a combined form of segmental enterocolitis The terminal ileum showed the typical x ray findings associated with regional ileitis She continued to do well and worked as an active secretary At age 36 8 years after onset of symptoms an exacerbation marked by persistent vomiting abdominal cramps and weight loss necessitated hospitalization X ray studies showed pronounced narrowing of the jejunum just distal to the ligament of Treitz extending for about 10 cm Below this the jejunum was dilated and the mucosa irregular In the terminal ileum the lumen also was narrow and rigid and the mucosa destroyed The ileal and colonic lesions were unchanged from previous examinations The newly developed jejunal obstruction was treated medically because operative therapy appeared unpromising in such widely disseminated ileocolitis Improvement was temporary and persistent vomiting recurred At operation three distinct zones of involvement were noted The jejunum was stony hard and narrow beginning immediately distal to the fossa of Treitz and extending into the beginning of the small intestinal mesentery Distally a segment of small intestine was dilated and somewhat thick The stony hardness led to suspicion of carcinoma but resection was impossible

*Autopsy revealed granular cobblestone jejunal mucosa just distal* to the ligament of Treitz with thick submucosa and muscularis In the center was an ulcerated polypoid flat based encircling carcinoma measuring 5 cm which extended directly into the mesentery Microscopic examination showed adenocarcinoma

CASE 2—Man 30 had acute obstruction of the upper small intestine For the previous 19 years he had recurrent abdominal cramps nonbloody diarrhea and weight loss At age 18 he had been told he had ulcerative colitis and was treated with sedation and a low residue diet with good results but symptoms recurred at age 19 after induction into the army On admission x ray studies revealed an inflammatory disease limited to the upper jejunum After decompression of the bowel and re establishment of normal fluid and salt balance laparotomy revealed a series of stenosing lesions in the proximal jejunum with extreme dilatation of the bowel between them

( ) Am J M d. 23 493-498 S ptembe 19 7

Pathologic examination revealed that the zones of constriction were due to presence of typical regional enteritis. At the junction of one constricted zone with dilated segment an unusually firm indurated nodule was discovered and histologic examination revealed papillary adenocarcinoma Liver biopsy revealed metastatic carcinoma resembling that of the jejunum Death occurred a few months later with generalized carcinomatosis

Of 13 patients with carcinoma of the jejunum seen at 2 hospitals over a span of 10 and 30 years respectively 2 were patients with regional jejunitis Such incidence suggests a causal relationship between these two conditions

**Follow up on 200 Patients Treated for Hirschsprung's Disease during a 10 Year Period** is reported by Orvar Swenson[3] (Boston Floating Hosp for Infants and Children) In these children the normal appearing but aganglionic and functionally defective terminal segment of colon had been resected and intestinal continuity then restored

Of the 6 postoperative deaths 4 occurred in infants There fore resections are now postponed until age 12 18 months with the patients maintained by colostomy until then Further postponement is impractical because of difficulties encountered in bowel training

In the survivors 17 major and 17 minor complications were encountered Nine had strictures at the anastomotic site ascribed in 6 to prolonged deactivation and consequent narrowing of the colon distal to a transverse colostomy Eight of the strictures were dilated one had to be resected

Two patients in whom gross leaks of the anastomosis developed required emergency colostomy which was later closed 1 had a slough of 10 in of terminal colon which was later reconstructed Of 73 patients followed 5 10 years all but 1 have had complete relief from symptoms and are normal The 1 unsatisfactory result is in a boy who has recurrent attacks of gastroenteritis although general health is excellent Incontinence has not been a problem Of 64 patients followed 2 5 years all but 1 are perfectly normal The unsatisfactory result is in a child who did well for 1 year and then began having chronic diarrhea Among the 52 patients operated on during the past 2 years results were good in 49 One child continues to have some constipation and 2 have recurrent diarrhea

The most distressing finding was that 1 5 years after op

(3) Ann. S g 146 06-714 Oct ber 1957

eration 7 children died suddenly after an illness of less than 24 hours duration In the 6 in whom autopsy was performed infection with severe dehydration was the cause of death This experience plus the fact that such sudden deaths occur in patients before operation suggests that some infants and to a less extent children with Hirschsprung s disease have some defect in the normal mechanisms to combat infection

Removal of the pathologic colon down to within 2 cm of the mucocutaneous margin can be accomplished without dis turbance of ejaculation or fecal continence Unless this amount is removed the symptoms will not be relieved

**Early Lesions in Ulcerative Colitis** George Lumb (Univ of Tennessee) and R H B Protheroe[4] (Westminster Hosp London) studied surgical specimens in which only part of the colon was diseased Resection had been necessary be cause of serious disease and because radiography had shown spread to fresh areas of colon At the junction of normal and abnormal areas the histology of grossly normal portions was carefully noted because in these areas the earliest le sions of the disease might be expected

The colon was partially involved in 41 specimens Total colectomy had been done in 29 and partial resection in 12 After surgical removal small gross focal abnormalities were found in 22 of the 29 total colectomies in areas which had been considered radiologically normal The junction be tween normal and abnormal mucosa was never abrupt but changed gradually covering an area of several centimeters Diffuse ulceration gave way to discrete lesions with ap parently normal mucosa between

Group 1 lesions were normal to the naked eye but histo logically the crypts of Lieberkuhn were plugged with poly morphonuclear leukocytes surrounding capillaries were mildly dilated and the lamina propria was infiltrated with lymphocytes

Group 2 foci varied from red spots to small erosions and frank ulcers surrounded by pale normal looking mucosa Histologically there was progression from group 1 Single or adjacent groups of cysts sometimes became grossly dis tended with pus cells in the lumens (Fig 89) The cells lining these crypts showed degenerative changes vacuo

(4) Gast oent l gy 33 457-474 S pt mbe 1957

lated cytoplasm breakdown of nuclei loss of cell outline and neutrophilic infiltration

The earliest active lesion thus seems to develop in the bases of the crypts As necrosis progresses small erosions establish continuity between the lumen and the submucosa The accumulation of neutrophils with eosinophils red blood cells serum and mucus in the lumen of the crypts constitutes the so called crypt abscess a characteristic of ulcerative colitis Excessive infiltration by eosinophils was seen



F g 89 —Sm ll g p f c ypt g ly d t d d w th p lls h w g b ak th gh t und ly g bm H m t yl n eo duc d f m x 0 (Court f f Lumb G nd P th R H B G t oe t l gy 33 457-474 S pt mbe 1957)

in a third of the cases In larger lesions numerous crypts are involved Large areas of the walls break down infective material is liberated into the submucosa and ulceration is wide spread These ulcers are rarely clear cut and usually present an irregular pattern of necrotic debris and inflammatory cells

Group 3 lesions were ulcers as deep as the muscularis mucosae The inflammatory exudate often involved the submucosa The intact cells in the surrounding epithelium differentiated into increased numbers of goblet cells which poured out an excess of mucus coating adjacent mucosa The lamina propria was edematous and the capillaries di

lated and congested The degree of capillary engorgement was not correlated with spread or severity of inflammation

No primary lesions were found in vessels in the wall of the bowel or the adjacent mesentery which could be construed as causative When sufficiently advanced to form frank isolated ulcers the lesions tended to a linear arrangement but were not correlated with the taeniae coli Had basement membrane changes been significant they should have been demonstrable in intact mucosa before erosions or ulcers had developed No such changes were found in fresh fixed *material from surgical specimens Basement membrane* changes common in the ulcerative phase are probably post inflammatory Vascular abnormalities are either secondary to the inflammation or coincidental degenerative changes

Ulcerative colitis usually begins in that part of the colon most constantly subjected to minor traumas A specific extrinsic cause is unlikely A variety of intrinsic and extrinsic stimuli may suffice to produce spreading ulceration of the colonic mucosa

► [This study supports the contention of Warren and Sommers (J A M A 154 189 Jan 16 1954) that the essential histologic feature of ulcerative colitis is a small abscess in the base of the crypts and that the diffuse inflammatory reaction we are apt to associate with the disease represents an advanced process complicated by secondary infection and tissue reaction Microscopic crypt abscesses moreover may involve portions of colon mucosa that appear grossly normal —Ed ]

**Course of Nonspecific Ulcerative Colitis Review of 20 Years Experience and Late Results is reported by** Benjamin M Banks Burton I Korelitz and Louis Zetzel (Harvard Med School) Of the 245 patients treated follow up is available in 244 for an average of 12 1 years and 73% have been followed 11 years or more since the onset of the disease In 64% the colitis was classified as severe or extremely serious with marked toxemia hemorrhage or perforation at the time of the first or subsequent hospital admissions In 9 cases the disease was present in 2 or more members of the immediate family an incidence of 3 7% Epidemic diarrhea due to proved bacillary dysentery or salmonella infection initiated the first attack or an exacerbation of the colitis in 8 cases Whereas others with such diarrhea recovered those who acquired ulcerative colitis had persistent symptoms and finally showed the classic manifestations of the disease

Multiple complications tended to occur in the same pa

(5) G t l gy 32 983 1012 Ju 1957

lated cytoplasm breakdown of nuclei loss of cell outline and neutrophilic infiltration

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F g 89 —Sm ll g p f ypt g o ly d te d d w th p cells h wing b eak th gh t und l g bm H m t yl n eo duc d f m x70 (Courtesy of Lumb G d P th R H B G t oe terol gy 33 457 474 Sept mbe 1957)

in a third of the cases In larger lesions numerous crypts are involved Large areas of the walls break down infective material is liberated into the submucosa and ulceration is widespread These ulcers are rarely clear cut and usually present an irregular pattern of necrotic debris and inflammatory cells

Group 3 lesions were ulcers as deep as the muscularis mucosae The inflammatory exudate often involved the submucosa The intact cells in the surrounding epithelium differentiated into increased numbers of goblet cells which poured out an excess of mucus coating adjacent mucosa The lamina propria was edematous and the capillaries di

earlier ileostomy or colostomy was performed in 8 patients The decision in each case was apparently made *ad hoc* when the clinical features seemed favorable One patient is well 3 died as a direct result of the operation and 4 required new ileostomies or colostomies because of severe exacerbation of the disease with 1 of these another operative death

Late results are given in the table Of the 51 who died 40 succumbed to ulcerative colitis or one of its medical or surgical complications including carcinoma This developed in 9 patients an incidence of 3 7% and in all was in the distal colon or rectum The proportion of patients relatively well

LATE RESULTS IN 244 CASES OF ULCERATIVE COLITIS

| Outcom | of P ents | Per Cent |
|---|---|---|
| A ympt m ic g ry | 43 | 17 6 |
| M ld ac bat g ry | 48 | 19 7 |
| Se ac b t g ry | 43 | 17 6 |
| A ymptom —f n t on g l ost my | 40 | 16 4 |
| Ileost m dysf t | 6 | 2 5 |
| A ymp m t —f t g colost my | 1 | 0 4 |
| C lost my dy f tio | 2 | 0 8 |
| Oth d sease† | 10 | 4 1 |
| Died—all se | 51 | 20 9 |
| Total | 244 | 100 |

Of the 46 p t ent 19 h h d mor le tomy on
†P t t wh h d th maj d w th 1t ondary p bl m

on medical management alone was approximately the same (40%) for all age groups About half of those whose disease began in the first 2 or last 2 decades required major surgery for colitis

Segmental colitis was diagnosed in 17 patients (7 7%) The clinical course was similar to that in the series as a whole in frequency and severity of exacerbations incidence of complications and mortality Systemic manifestations including arthritis erythema nodosum and pyoderma were relatively more frequent in patients with right sided colitis

Films of the colon were taken at various intervals In patients whose disease was originally limited to the rectum and left half of the colon the process progressed proximally in 47% about 25% showed a localized increase in the destructive processes 9% showed no change and 17% were improved Most patients who had right sided involvement showed extension distally with successive attacks Prognosis could not be correlated with extent of initial involvement

tient Serious colonic complications appeared in 5 10%, skin lesions in 13% and arthritis in 16% Anal and rectal diseases developed in 48% The concurrent diseases were most frequently peptic ulcer chronic cholecystitis cholelithiasis and allergic disorders but their incidence was the same as could be expected in the general population for similar ages and sex Cirrhosis of the liver was rare

The more seriously ill patients were divided into two groups those treated before and those treated after chemotherapy was available Excellent results were obtained in 37% of cases treated supportively and in 52% after antibiotics and chemotherapy were added to the regimen Frank failures were 30% and 16% respectively The differences in response were less impressive when all gradations of therapeutic benefit were compared The incidence of bacterial complications such as pyogenic lesions of the skin perianal infections pericolic abscess perforation of the intestine peritonitis and septicemia was almost identical Thus chemotherapeutic agents and antibiotics while apparently responsible at times for initiating a dramatic remission were unreliable and inconsistent in their beneficial effect on both the immediate and long term course of the disease Erythema nodosum occurred far more frequently in patients treated with antibiotics and chemotherapy Of the entire group 52 received some form of antiamebic therapy empirically at some time Two seemed to benefit though stool examinations for amebas had been consistently negative The other 50 patients showed no appreciable response

The medical mortality was 12 in 240 cases Another 12 patients almost dead when operated on died shortly thereafter and probably should be considered medical deaths A more accurate mortality would be 5 10%

Of the total 245 patients 84 (34%) required some form of surgery The results of ileostomy performed in 40 cases showed a mortality of 25% Because of continuing massive bleeding 4 patients required early secondary subtotal colectomy as an emergency measure and 3 of these died In all 15 patients died after ileostomy 10 after the primary procedure and 5 after subsequent operations Only 8 of the original 40 improved and remained well without further definitive surgery

Operation to restore continuity of intestinal flow after an

nosis of pericolitis and peritonitis often is made during the course of ulcerative colitis Incidence of such cases improv ing and surviving is difficult to determine because conclu sive evidence of perforation is lacking in most

► [The low incidence of perforation—with or without steroid treatment—attests to the expert care that patients with ulcerative colitis receive at the Univer ity of Chicago Clinics As the authors themselves indicate how ever perforation is often a matter of definition If pericolitis and local peritonitis are ob erved near a colonic wall that is paper thin but exhibits no frank hole is it a perforation or is it not?—Ed ]

**Ileostomy Chemistry** B N Brooke[7] (Birmingham Eng land) collected material from the ileostomy of patients with ulcerative colitis throughout 24 hours and determined ni trogen sodium potassium and calcium content Each pa tient had to be treated according to his particular require ments for replacing fluids and electrolytes In general fluids alone were given intravenously until the ileac stoma began to function usually about 24-48 hours after operation when oral intake was started at 30 ml hourly and increased slowly to a light diet by the 5th day

Patients with ileac stoma remain in negative balance for nitrogen no longer than do patients who undergo other types of operations Thereafter nitrogen balance is positive In ulcerative colitis more nitrogen may be lost preopera tively in the stool than subsequently from the ileac stoma One man lost 7 Gm daily before surgery which was re duced to 1 2 Gm afterward The maximum in absence of complications was 3-4 Gm lost each day immediately after ileostomy declining to 1 2 Gm later Therefore nitrogen loss has little significance because normally 1 Gm is the average daily amount in the stool Characteristically large amounts of fluid are lost through the stoma reaching 2 L or more daily during the 1st postoperative week decreasing to 500 ml daily and remaining at 250 500 ml The volume of fluid excreted is directly correlated with the quantity of sub stances contained in the excreta especially nitrogen and sodium

At first sodium loss is 200-400 mEq /L which invari ably exceeds the previous loss with diarrhea As the stomal discharges thicken the rate of loss decreases to about 150 mEq /L The large early loss may deplete the body of so dium and induce a sudden clinical collapse This is best treated prophylactically by routine intravenous therapy

(7) D Col & Rect m 1 3 14 J F b 1958

The course of the patients may be summarized about 20% have been well in terms of the colitis 20% have had occasional mild recurrences 20% severe exacerbations 17% have been relatively asymptomatic after definitive surgery 3% have a malfunctioning ileostomy and 20% are dead
► [A follow up of 244 out of 245 patients treated is a remarkable feat! —Ed ]

**Role of ACTH and Adrenal Steroids in Perforation of Colon in Ulcerative Colitis Clinical Pathologic Study** Moshe B Goldgraber Joseph B Kirsner and Walter L Palmer[6] (Univ of Chicago) compared incidence of perforation in the periods before and after use of steroids and the histologic features representative of the perforations in each group

Of 730 patients with ulcerative colitis seen between 1929 and 1956 12 (1 6%) died of perforation of the bowel into the free peritoneal cavity and peritonitis Before the era of ACTH and adrenal steroid therapy peritoneal reaction in patients with colon perforation was not pronounced In 1 patient perforation was not even suspected and in another diagnosis was made during x ray studies Incidence of perforation in the presteroid period was 2 5% After 1950 incidence among patients treated with steroids was 1% This reduction is not statistically significant but certainly indicates no increase in mortality during ACTH and corticoid therapy

A striking histologic feature was the presence of organized thrombi in small venules found in 7 of 10 patients examined Thrombophlebitis often is mentioned in ulcerative colitis but reported incidence varies from 1 9 to 7% No inflammation of arteries was found although an occasional unimpressive perivascular infiltration was evident The arterioles often had thickened walls and a slitlike vascular lumen similar to the changes seen near other chronic processes

The high incidence of perforation which has been reported by others was not confirmed by this study Surgery is not essential when perforation has occurred because many survive with medical management alone In patients with colonic perforation treated with or without steroids there was no discernible significant difference in the cellularity of the colonic mucosa in the fibroblastic proliferation nor in the leukocytic accumulation in the inflamed serosa Diag

(6) G st e t ol gy 33 434 456 S pt mbe 1957

or more polyps in the rectum and/or colon In another 586 (7 7%) rectal or colonic polyps were found on subsequent examinations altogether 1 462 patients (19 2%) A total of 2 363 polyps were found among 1 459 patients Biopsy was done on only 454 of the lesions Most were benign adenoma 3 showed malignant change without invasion and 12 showed malignant change with invasion or were frankly adeno carcinoma Usually biopsy was done only on polyps over 5 mm in diameter About a third of the polyps seen by proc tosigmoidoscopy were in the posterior quadrant 91 5% were under 5 mm in diameter and half were under 3 mm Of the 876 patients with polyps noted at the first examination 237 (27%) showed 2 or more lesions Of the total 1 462 pa tients 62% had single lesions The male female ratio of pa tients with polyps was 1 56 1

In the age groups 45 54 55 64 65 74 and over 74 inci dence of polyps was 18 19 8 25 and 20% respectively No significant correlation was noted between incidence of pol yps and incidence of diverticulosis diverticulitis achlorhy dria hypochlorhydria seborrheic keratoses senile keratoses nevi lipomas and leukoplakia Incidence of bleeding per rectum was only 3 2-4% and was higher in patients in whom polyps had disappeared or had been removed strongly sug gesting that the polyps discovered by endoscopy were not the source of bleeding In patients with polyps above the sigmoidoscoped area incidence of bleeding was 12 5% The polyps were larger and probably were related to the bleeding

Many tiny adenomas disappeared without treatment and were not seen by 2 or more examiners on successive annual follow up examinations One of these lesions was 8 mm and 1 was 40 mm in diameter Nineteen polyps in 18 patients showed signs of growth in 1 or more years between exam inations In 1 patient an untreated unbiopsied tiny lesion grew until it was large enough to biopsy and then proved to be malignant

The study suggests that if a patient has a polyp or polyps discovered by proctosigmoidoscopy chances of having a polyp or polyps discovered by barium enema in the proximal colon are 4 5% (3 7% with a single lesion 6 6% with 2 or more) The chances of discovering frank carcinoma by ba rium enema in the proximal colon are 0 34% if polyps are seen by proctosigmoidoscopy The chances of more polyps

within the first 4 5 postoperative days For rule of thumb calculations the daily volume of output from the stoma may be assumed to contain 300 mEq sodium/L When sudden collapse occurs it should be assumed to be due to salt depletion and treated urgently and rapidly with double strength saline solution intravenously

Potassium loss is more urgent preoperatively because of large fecal loss In 5 of 7 patients studied immediately after ileostomy excretion did not exceed 20 mEq daily in contrast to 35 85 mEq before surgery Potassium loss is not a therapeutic problem after ileostomy Indeed ileostomy may have to be expedited to check this loss Potassium loss may be assumed among patients who have ileostomy diarrhea and those with secondary ileitis in whom daily loss may reach 30 mEq /L

Total daily sodium loss through the ileac stoma and urine is reduced considerably among patients receiving cortisone because of reduced volume of ileal effluent total loss of potassium also is less Cortisone may be indicated after operation in patients who lose large volumes and therefore large amounts of sodium

Calcium loss is of no immediate concern because reserves of the body are so large More important is daily loss with an established ileac stoma in patients taking a normal average diet In these daily loss may be 50 60 mEq or just over 1 Gm which is more than a normal person on an average diet loses daily in the stools (0 4-0 8 Gm ) Positive calcium balances were however demonstrated in 4 patients including 1 late in pregnancy

► [Only one different interpretation may be added to these valuable data perhaps it would be more proper to say that the quantity of nitrogen and sodium lost in ileal discharges is correlated with volume of fluid lost rather than implying a reverse causal relationship —Ed ]

**Incidence and Significance of Polyps of Colon and Rectum** A high incidence of asymptomatic polyps has been found in the sigmoid in patients aged 45 or over in routine proctosigmoidoscopies at the Cancer Detection Center of the University of Minnesota Irving F Enquist[8] reviewed the findings in the 7 608 patients examined between 1948 and 1956 Most patients were re examined at 1 or more annual follow up visits

At the original examination 876 patients (11 5%) had one

(8) S g ry 4 681 688 O t be 1957

elderly persons of all degrees of intelligence One cause was inadequate insertion of the tube, less than 4 in being considered inadequate

Three fourths of the patients took an hour or less for total colostomy care The others took 1 3 hours except 1 who took 4 5 hours once a week Half the patients used no medication around the colostomy area More than half used the aluminum dome with or without fluff pads to cover the colostomy About 25% used colostomy bags contrary to the recommendations of the hospital group No covering except undergarments was used over the colostomy by 3 Of 38 patients 21 reported no or little spilling Precautions to avoid spilling were mainly change of diet—avoidance of stimulating foods—or waiting longer for complete return of the enema The foods most often considered stimulating were cabbage beans raw and dry fruit sour items beets fats and soda pop

Most patients stated that avoiding gaseous foods such as cabbage beans and onions prevented colostomy gas Some irrigated more thoroughly the day after the bowel was upset which cleared the gas In 15 gas was troublesome Colostomy odors were a bother or were present in 35 Among the 15 who used colostomy bags 11 were bothered by odors though hygienic means were used to prevent them Avoiding chocolate candy or eggs decreased the odor in several

Constipation reported by 7 was controlled by mineral oil in each Diarrhea was severe in only 5 Food was considered the biggest causative factor the offenders in order of frequency being beans cabbage sauerkraut fresh fruit rich foods raw or coarse foods sugars onions spicy foods and alcohol Foods considered to cause constipation were cheese boiled milk potatoes starches fresh white bread and chocolate Cabbage strawberries fresh white bread milk and starchy foods were each mentioned by both groups as causing diarrhea or constipation

Social life had decreased after colostomy in nearly all patients Most had fewer visitors and did less traveling and community work and many spent more time at home Of 62 only 19 actually blamed the colostomy and 8 said it was only partially to blame Work capacity was considered to be decreased by 30 patients 14 did less heavy work and 2 could

being discovered are 22% and the chances of lesions recurring at the site of destruction are 27%

Polyps discovered by barium enema were removed but 6% of the patients revealed additional lesions at follow up barium enema Among the 1 462 patients 27 with a satisfactory barium enema study reportedly negative subsequently showed a polyp or cancer in the colon on repeat barium enemas Of the 48 operated on for polyps seen by barium enema 10 had more polyps at operation than were seen by x ray

Whether or not each lesion discovered represents a possible malignancy cannot be answered even though it has been claimed that all these adenomatous polyps and papillomas are truly precancerous Incidence of malignancy by biopsy was about 1% but this pertains to the larger lesions only As incidence of malignancy definitely increases with size of the polyps in the tiny lesions it must certainly be less than 0 5%

If routine subtotal colectomy had been done in each patient with colonic polyps noted by x ray incidence of multiple lesions would have been higher Subtotal colectomy probably is justified since the operation is nearly as easily done as segmental resection the early and late morbidity is no worse and if the polyps are precancerous their removal will have been complete

**Results of Questionnaire Survey of Colostomy Patients** are reported by Robert J Samp[9] (Univ of Wisconsin) The data were compiled from 92 detailed questionnaires Sex ratio of respondents was equal time since operation varied from 6 months to 27½ years and ages ranged from 22 to 84 years with most aged 50 70

Colostomy irrigations were done daily by 65% every other day by 15% and infrequently by 8% none at all were done by 12% Most persons preferred warm plain irrigating water 2 used boiled water and 20% added soap salt soda or some combination of these Most who added soap reported incomplete cleansing and rapid emptying time of the colostomy Only 15% of those who irrigated reported improper cleansing incomplete irrigation or that they were never properly cleaned out This percentage of failures seems understandable in a group including many

(9) Su g Gy ec & Ob t 105 491 497 Octobe 1957

most entirely absent in over 2 400 tests Of 44 serologically positive cases 6 were confirmed by evidence of abscess or long illness that responded to treatment though the stools were never positive Many tests were unsatisfactory because attempts were made to read serums which were not clear before adding antigen Spontaneous precipitation occurs under some conditions of aging storage and handling of serum

Some asymptomatic carriers have enough invasion to produce or maintain a detectable level of antibody The test is positive in 45 60% of asymptomatic carriers If serum is obtained early in the disease shortly after first invasion of tissue the test should be negative if serum is obtained late all tests should be positive In relapse or reinfection the time of appearance of antibody will be shortened In small series of cases of acute amebic dysentery the precipitin test was positive in 9 of 22 trials

After successful treatment of the disease the test becomes negative usually in a few weeks It becomes positive with every relapse On treatment the degree of positivity may increase briefly which has been ascribed to the antigenic stimulus of sudden death and disintegration of large numbers of amebas in the tissues This increase confirms the diagnosis

Even if E histolytica is unquestionably found in a fecal specimen the physician may not always be able to attribute the symptoms to the parasite No immunodiagnostic method can do more than detect antibodies when they are present In amebiasis a good serologic test should be negative until the tissues are invaded and antibody formation stimulated In acute amebic dysentery especially early reactions should be negative When tissue invasion has presumably occurred in other than acute amebic dysentery the test is 85 100% positive In serums which are clear initially false positive results virtually do not occur

► [The validity and clinical usefulness of this test are still under trial as evidenced by two divergent views expressed in Gastroenterology 30 535 1956 and 33 123 1957—Ed ]

do more Three lost their jobs because of the colostomy One stated that his employer told him that he was no good after the operation and the other 2 gave no reason Nine quit work because of the operation

In 2 marriage had suffered and in 3 marriage was some what affected Twenty three reported changes of sexual na ture and 9 7 of whom were women refused to answer this question The colostomy mechanically interfered with sexual activity in 5 and 2 considered it bothersome

Only 7 stated that the operation had not been fully ex plained to them Of 55 who commented on their reactions to the announcement that colostomy was necessary 51 said that they adjusted to it in a short time

► [When a surgical procedure involving the creation of an external stoma of the bowel is contemplated particularly if the cause of the patient s ill ness is not malignant one of the imponderables that confronts the physi cian is how will the procedure affect the patient s life and how will he react to it? This frank analysis of what happens is reassuring in that it shows a satisfactory adjustment by the great majority of patients with colostomies Some unhappy individuals become recluses because they can not control the escape of noisy or odorous gas from a colostomy but does not even the normal sphincter Ogilvie s sentinel of social security suffer similar mishaps?—Ed ]

**Serologic Diagnosis of Amebiasis by Means of Precipitin Test.** A specific and sensitive serologic test for antibodies to Endameba histolytica usable in any medical laboratory would be helpful Jeanne C Moan[1] (Lansdowne Pa ) pre sents a new rapid and simple test

Methods —Endameba histolytica obtained from NIH strain 103 are maintained in a medium free from human bacteria and consisting of liver concentrate disodium phosphate potassium acid phosphate sodium chloride Bacto Proteose Peptone and distilled water The parent culture is subcultured and spun gently The supernate is de canted and the packed amebas transferred to a centrifuge tube The amebas must be intact and motile The mass of amebas is then frozen at —10 C for 24 hours to rupture the amebas and thawed. The resultant material is centrifuged at approximately 12 000 rpm in an angle centrifuge until the supernatant is clear The supernate is the raw antigen ready for titration Merthiolate® is added 1 10 000 and the product is stable for 5 years

For the test 0 5 ml serum is sufficient centrifuged at 2 000 rpm and inactivated at 56 C for 30 minutes The antigen is incubated at 37 C for 15 minutes On a paraffin ringed slide 0 05 ml serum is placed and 0 05 ml antigen added then mixed thoroughly for 4 minutes The test is read immediately microscopically through the closed iris diaphragm for intensity of precipitate

The test is highly specific False positive results were al

(1) Am J Tr p M d 6 499 513 May 1957

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# LIVER AND GALLBLADDER

**Bilirubin Metabolism in Jaundice** is reviewed by Barbara H Billing (Postgrad Med School London) and G H Lathe[2] (Univ of Leeds) The formation of bilirubin from the breakdown of hemoglobin occurs in the reticuloendothelial system Bilirubin is then transported in the plasma to the liver which excretes the pigment in bile Passage through the liver produces some change in the bilirubin which is detectable by the direct van den Bergh reaction

The difference between direct and indirect reacting bilirubin has now been clearly established to be due to the formation by conjugation of bilirubin/diglucuronide The conjugation of lipid soluble bilirubin with glucuronic acid results in formation of a water soluble pigment which gives a direct van den Bergh reaction Bilirubin also reacts directly if it is converted to its sodium salt or if solvents such as ethanol which are miscible in both water and chloroform are used The essential factor appears to be the solubility of bilirubin in water Glucuronide conjugation of bilirubin has been demonstrated in the human dog rat and guinea pig

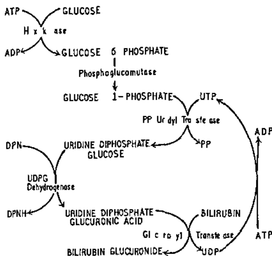
Normally the liver converts bilirubin to conjugated bilirubin probably in the parenchymal cells The mechanism is unknown Newly formed liver cells can extract and secrete bile pigments as well as older cells Liver tissue homogenates and slices will conjugate bilirubin in the presence of uridine diphosphate glucuronic acid which acts as a glucuronyl donor in many glucuronide syntheses Conjugation is active in the microsome fraction of liver homogenates A possible mechanism is outlined in Figure 90 Extrahepatic conjugation of bilirubin to the monoglucuronide has been demonstrated but the site remains unknown

In obstructive jaundice and hepatitis bilirubin bilirubin monoglucuronide and bilirubin diglucuronide are found in the blood Both mono and diglucuronide conjugated bilirubin appear in the urine but not bilirubin There seems to be no simple relation between the total amounts of pig

(2) Am J M d 4 111 121 Ja y 1958

ment in plasma and in urine possibly because the renal threshold changes

In hemolysis bilirubin production due to hemoglobin breakdown may be increased as much as 5 15 times The normal liver can excrete the bilirubin equivalent of all the hemoglobin in the body in 10 12 hours This capacity therefore limits the rise in plasma bilirubin to 2 5 mg /100 ml plasma In hemolytic jaundice the chief bile pigment in the




F g 90 —P bl m h m f co j g t f b l rub w th gl d (C t y f B ll g B H d L th C H Am J M d. 4 111 1 1 J y 1958 )

plasma is bilirubin but small quantities of mono or diglucuronide conjugated forms are responsible for the direct reactions detected The presence of these conjugated pigments suggests some liver derangement which appears to be relatively specific since alkaline phosphatase levels in plasma are normal

The dominant pigment in neonatal jaundice is bilirubin The rate of red cell breakdown is not greatly elevated The absence of conjugated bilirubin in the plasma suggests a metabolic block in the excretory process The bilirubin conjugating capacity is low even in the presence of added glucuronyl donor *Apparently bilirubin glucuronyl transferase activity is defective at birth* Before birth the placenta

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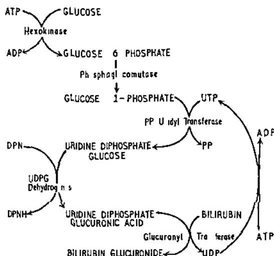
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not the liver is responsible for removing bilirubin Jaundice appears only if the responsible liver enzyme system has not matured In small and premature infants with immature livers the plasma bilirubin tends to rise to considerable heights Because of this enzyme deficiency many newborn infants particularly those with hemolytic disease are exposed to higher plasma concentrations of unconjugated bilirubin than ever attained in the adult though the adult may have total pigment concentrations of similar amplitude

The high levels of bilirubin in the premature infant with hemolytic disease or familial hyperbilirubinemia may result in kernicterus The primary cause of this brain damage is bilirubin and the toxicity is probably related to the lipophilic nature of the pigment This would explain the absence of kernicterus in the severely jaundiced adult since the dominant plasma bile pigments are the water soluble bilirubin glucuronides which do not stain brain tissue

**Possible Effect of Hydrocortisone on Bilirubin Excretion by Liver** Harry Shay and David C H Sun[3] (Temple Univ ) studied 10 patients who had T tube drainage after cholecystectomy and choledochostomy for chronic cholecystitis and stones in the gallbladder common duct or both Only patients with normal sized common bile ducts and normal liver function profile were accepted for study Investigations were usually made 6 8 days postoperatively and after serum bilirubin and alkaline phosphate levels had returned to normal

METHOD —Specimens of T tube drainage were collected for 30-minute periods for 1 hour before and 4 hours after the drug or control injection On the day of the control test intravenous infusion of 200 ml of 5% dextrose in distilled water was given in 1 hour On the day of drug study 100 mg hydrocortisone (free alcohol) was dissolved in 200 ml of 5% dextrose in distilled water and given intravenously in 1 hour The duodenal contents were collected by continuous suction at negative pressure equivalent to 76 cm water through a Rehfuss tube with the tip in the metaduodenum at the same time the T tube drainage was being collected Bromsulfalein 2 mg /kg was injected intravenously in 5 patients Since no dye was recovered from the duodenal tube aspiration of bile through the T tube from the common bile duct must have been complete

The data on total bilirubin output showed significant differences among patients and among periods of collection ($P<0.05$) but none of the differences between control and hydrocortisone studies was significant at the 5% level The

(3) New Engl J Med 257 62 65 July 11 1957

means of total bilirubin output for control and hydrocortisone studies were 4 31 and 4 12 mg clearly indicating little or no difference Likewise no significant effect on volume or bilirubin concentration was noted after hydrocortisone These studies fail to demonstrate a hydrocholeretic or choleretic effect of hydrocortisone on bile secretion from the liver during the 4-hour test period

► [Another study (J Lab & Clin Med 51 701 1958) not only confirms that intravenous hydrocortisone given over short periods of time does not affect T tube output of bile volume and bilirubin in choledochostomized patients but that other aspects (note how that overworked word parameters is being avoided) of hepatic secretory function appear unchanged when cortisone is given orally for several days Although additional studies in our laboratory indicate that removal of radioiodine labeled rose bengal (radio-rose we call it) from the liver may be affected by adrenal steroids the phenomenon is inconstant and limited in degree The idea that adrenal glucocorticoids act as choleretics in normal persons should be abandoned. —Ed.]

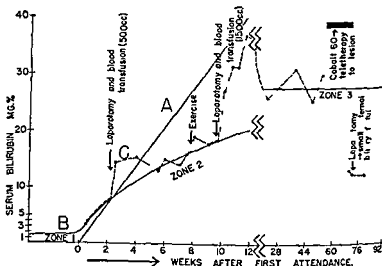
**Rise in Serum Bilirubin with Biliary Obstruction and Its Decline Curve after Operative Relief** was determined by *F F Rundle D Perry M Cass and T H Oddie*[4] (Royal North Shore Hosp Sydney) The phase of increasing bilirubinemia was analyzed in a single case

Man 48 lost 7 lb in 6 weeks The only definite finding was slight tenderness in the right hypochondrium No icterus was noted on initial examination but the next day he had pruritus slight jaundice pale stools and dark urine At laparotomy 2 weeks later a carcinoma at the junction of the hepatic ducts was found with a collapsed gall bladder and common duct A second operation 7 weeks subsequently showed complete blockage of the biliary tract at the porta hepatis with tremendous dilatation of the left hepatic duct above the block.

The changes in serum bilirubin (curve *C* Fig 91) are compared with the expected rise in complete obstructive jaundice (curve *A*) and complete on partial obstruction (curve *B*) In curve *A* it was assumed bilirubin production is maintained at normal 250 mg daily resulting in a daily increase of 0 5 *mg serum bilirubin daily in a total body wa*ter of 50 L In complete on partial obstruction the serum bilirubin rises imperceptibly over weeks or months as anatomic obstruction increases but resulting physiologic mechanisms compensate for it When the block becomes complete compensation is no longer possible indicated as zone 2 During this time the rate of increase is progressively slowed because increasing amounts are excreted in the urine When this excretion equals the daily production of bilirubin a

(4) S g ry 43 555 56 Ap 1 1958

plateau (zone *3*) is reached The height of this plateau about 30 mg /100 ml in the case presented varies with each patient s ability to clear bilirubin in the urine The abnormally rapid rise demonstrated by the patient after laparotomy and




F g 91—R t f e um b l ub se n compl te b liary ob truct *A* theo t l c rv f eas aft sudden mpl te b truct at o t m a ming rmal bil p gm t p oduct on nd o u na y or otl e leakag *B* theo t cal c r e w th gr d lly in easing b tru t n beco m g complete t e o t m z ne *I* t l ft of o time one 2 from b t 0 t 20 w ks d o *3* f m 20 t 60 w k C rv *C* sh s ob ed l es f b l ub n n pat nt described d sugg t d rve sh w g tep e se w th e h of 2 p rat n F t pe t n l t d h u a d l u t (500 cc) f blood w s t a sf ed. Sec nd pe t la t d 4/ h u a d 3 unt (1 500 c ) of blood w re g v n

Becaus b rvati s w e p t a ted tim sc l nt upt d a d cha g d at 12 w ks *T I* th apy w th Co w gi n to gion of port h pat s and j t bo at 51 67 w ks F nal l pa to y w d 70 w ek aft b rv t ons bega and m ll t be was n rted w th d ffi ulty nto l ft h pat c d ct bo e porta Th t le d ed ly sm ll q ant e t b l (60 300 cc da ly) (C t sy f R dl *F F* *t I* Surg ry 43 555 562 Ap l 1958 )

blood transfusion can be explained only by abnormal loading of the serum with bilirubin Curve *C* rose stepwise with each of 2 operations

Decline in bilirubinemia was determined in 17 patients operated on for obstruction of the common bile duct due to gallstones in 14 and cancer of the ampulla of Vater or head of the pancreas in 3 In each a large tube inserted into the common duct insured free drainage of bile Bilirubin concentrations in serum and bile were determined serially In 24-hour specimens of bile the bilirubin is readily oxidized

to biliverdin and bacteria convert bilirubin into urobilin If collection is complete and gross infection is not present bilirubin estimated by the diazo method amounts to 80 100% of the total pigment and may be used as a guide to the general trend of bile pigment excretion

The liver was found to eliminate bilirubin efficiently In the absence of obstruction it quickly excreted the abnormal load resulting from major surgery despite a greatly reduced volume flow of bile after surgery Daily analysis of biliary

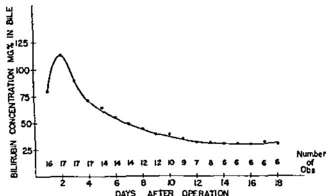



Fig 92—M n b l rubi co cent t on n b l d g ft h ledoch t my I 14 [ t t g llbladd h d been m ed. (Co t y f R dl F F t l Su g y 43 555 562 Ap l 1958 )

bilirubin in 17 patients relieved of obstructive jaundice showed a high concentration of bilirubin 2 days after operation (Fig 92) Serum bilirubin following operative relief of obstructive jaundice may exhibit a secondary rise 2 3 days after surgery but thereafter it declines exponentially with a half time of 17 4 days

► [The curves shown in Figure 91 although somewhat based on inference explain why jaundice may seem to come on suddenly and increase rapidly in patients eventually shown to have neopla tic obstruction of the major biliary passages In the early phases of a compl te-on part al obstruction (i e a progressive obstruction wh ch finally becomes complete) marked dilatation of the biliary tract abo e the ob tructing lesion may take place before any jaundice is noted by the patient or his fam ly

The statement that a plateau is reached in patients with complete biliary tract obstruction because renal clearance of bilirubin matches production of the pigment rema ns to be pro ed the authors are assuming this to be the ca e and give no data on the point. In contrast the exponent al decl ne of serum bilirubinem a following surgical relief of the obstruct ng process is neatly demonstrated.—Ed ]

**Fate of Bile Pigment in Cholera** The rice water stool of cholera is believed to be due to absence of bile pigment from the intestine caused by congestion and edema of the mucous membrane of the biliary tract K C Basu Mallik A Mondol and N C Ganguly[5] (Calcutta) studied 52 patients with cholera Stools examined soon after hospitalization showed no fecal urobilinogen in 37 patients and in the other 15 concentration was 0 07 0 52 mg /100 ml The pigment reappeared in the stools of all within 12 24 hours of hospitalization the average amount being 27 3 mg 7 days later this was 135 1 mg

Urine always gave a positive reaction with Ehrlich s reagent Serum bilirubin level on admission was 0 81 mg /100 ml corrected for hemoconcentration it was 0 63 mg Plasma hemoglobin concentration was not increased Serum alkaline phosphatase value was 8 6 King Armstrong units/ 100 ml

The usual explanation that absence of fecal urobilinogen is due to obstruction of the flow of bile caused by edema and congestion of the mucous membrane of the biliary tract is untenable No such confirmation was obtained in autopsies performed during the height of purging the alkaline phosphatase values were normal and the direct van den Bergh test was negative

It is most likely that bile pigment flows into the intestinal tract in cholera patients but is not detected because it is washed out or diluted to the point that it is not measurable Another possibility is that bilirubin is converted into a compound that does not react with Ehrlich s reagent The presence of Escherichia coli in the gut is necessary for conversion of bilirubin to fecal urobilinogen The temporary decrease in E coli at the onset of cholera may be responsible for failure to convert bilirubin into urobilinogen

► [The reasons for light colored stools in some patients with diarrhea but no jaundice is unexplained as is indeed the nature of much coloring matter in normal feces —Ed ]

**Urinary Excretion of Estrone Estradiol 17β and Estriol in Patients with Chronic Liver Damage** was studied by C B Cameron[6] (St George s Hosp Med School London) The healthy liver can remove biologically active estrogens from the metabolic pool The endocrine changes in patients with

(5) B t M J 2 803 805 O t 5 1957
(6) J Endocr 1. 15 199 205 J 1957

chronic liver disease were thus considered to be due wholly or in part to delayed inactivation of estrogen and consequent increase in estrogen activity Estrone has been isolated from bovine adrenocortical tissue and estradiol from human tes tes Potentiation of the action of such steroids could explain the endocrine features of cirrhosis in men and may even account for spider nevi and palmar erythema

Earlier work was based on bioassay of estrogen An ac curate chemical method for measuring the 3 important uri nary estrogens in amounts as low as 5 µg /24 hours has now become available These were determined in 9 men and 3 women all of whom were invalids but not moribund with diffuse liver fibrosis confirmed by biopsy All plasma albumin levels were below 3 Gm /100 ml

Total estrogen excretion was not increased in most of these patients In only 2 men and in no woman was the sum of the estrone estradiol and estriol greater than normal One man with increased excretion showed an increase in all 3 estrogens the other in estriol only Three other men and 1 woman excreted slightly increased amounts of estriol but total estrogen excretion was normal In 5 patients the ratio of estriol to estradiol plus estrone was higher than nor mal Unconjugated estrogen was not increased

These findings are contrary to data obtained by bioassay Perhaps 16α hydroxyestrone or some unidentified estrogen metabolites are biologically active and are increased in liver disease The excretion of estrogen is not well correlated with the clinical signs of estrogen abnormality The 1 man with gynecomastia did not excrete more estrogen than normal The men with increased excretion had no gynecomastia Ex cretion of estrogen was not increased more often in the pa tients who had ascites spider nevi palmar erythema or gastrointestinal hemorrhage than in patients who did not have these signs The view that impaired inactivation of es trogenic hormones is responsible for the endocrine features of liver disease cannot be considered proved

► [The finding of an abnormal level of a hormone or of a hormone metab olite in the blood or urine usually leads to speculations as to the relation of that level to some clinical manifestation of liver disease As the pre ceding and subsequent 2 abstracts show however abnormal levels may be influenced by technical limitations by alterations in the balance of produc tion vs disposal and by the volume of body fluid containing the measured substance At the same time these abstracts fortify the hope that abnor

malities of hormone metabolism in liver disease will eventually be ascribable to the breakdown of specific enzyme reactions.—Ed.]

**Metabolism of Thyroxin in Epidemic Hepatitis.** In previous studies A. Vannotti, Th. Beraud and J. Cruchaud[7] (Univ. of Lausanne) often observed that in epidemic hepatitis, especially if severe, there is an increase of circulating iodoprotein without elevation of basal metabolism, indicating that biliary elimination of thyroxin and, to a moderate degree, catabolism of thyroxin in the liver are diminished.

To confirm this fact with greater precision the fate of chromatographically pure thyroxin tagged with $I^{131}$ was followed after injection in small amounts (300-350 μc. radiothyroxin corresponding to 5-10 μg. thyroxin) into normal subjects and patients with epidemic hepatitis. Disappearance of radioactivity in plasma was followed 5 minutes, then 1, 3, 6, 9 and 24 hours after injection and each day during the 1st week, every 2 days the 2d week and on the 21st and 28th days. Daily elimination of $I^{131}$ in urine and feces was determined throughout the study. The value obtained 5 minutes after injection was taken as 100%. Fixation in thyroid and liver was followed by means of the scintillation counter.

In normal persons 50% of $I^{131}$ disappeared by the 7th day and in patients with epidemic hepatitis around the 9th day, showing that thyroxin catabolism is definitely slowed by a diffuse parenchymal hepatitis. Ten days after injection there was practically no radioactive thyroxin in the circulating blood, but a relatively large quantity remained in the blood of patients with epidemic hepatitis. Urinary elimination of thyroxin was normal in patients with hepatitis. In both normal and hepatitic subjects 50% of the thyroxin was eliminated by the urine 3 weeks after injection, whereas fecal elimination after a week in patients with hepatitis was only 4.6% of the injected thyroxin, contrasted with 10.3% in the normal. Radioactive counts over the liver showed reduced fixation in the hepatitic subject.

The prolonged circulation of thyroxin because of insufficient biliary elimination probably results from diminution of its deiodization in the injured hepatic cell and explains the higher level of plasma iodoprotein in epidemic hepatitis.

**Metabolism of Free and Conjugated 17-Hydroxycorticosteroids in Subjects with Liver Disease** was studied by Edwin Englert, Jr., Harold Brown, Stanley Wallach and E. L.

(7) G t oe te l g a 87 129 135 1957

Simons[8] (Univ of Utah) in order to evaluate the conjugating ability in such subjects and the metabolic pathway of cortisol degradation Twenty six intravenous infusions of cortisol were administered to patients with portal cirrhosis (15) viral hepatitis (3) metastatic carcinoma of the liver (1) postnecrotic cirrhosis (1) and cirrhosis with portacaval shunt (1) Groups of 3 to 9 subjects received infusions of the cortisol metabolites tetrahydrocortisone (Tetra E) dihydrocortisone (DiE) and tetrahydrocortisol (Tetra F) After infusion serial levels of free 17 hydroxycorticosteroids (17 OHCS) in plasma were estimated by the method of Nelson Samuels and Eik Nes and the conjugated 17 OHCS by the authors modification of the method of Bongiovanni

The mean half life of administered cortisol in the plasma was 229±19 minutes a significant elevation over the normal value of 112±5 minutes and there was no difference between subjects with and those without ascites A slower rate of removal from plasma was correlated with increased hepatic impairment as estimated by bromsulfalein retention After the infusion of cortisol levels of conjugated 17 OHCS in plasma rose for 2 hours to a mean maximum of 40 µg /100 ml This was slightly but significantly lower than normal ($P<0\ 05$) In subjects with ascites however the maximum was strikingly lower than normal

After infusion of cortisol metabolites plasma removal was much faster than after infusion of cortisol and appeared to be normal Levels of conjugated 17 OHCS reached normal maximums of 100-150 µg /100 ml at 0 30 minutes after infusion Again the concentration of conjugated 17 OHCS in plasma was consistently lower in subjects with ascites than in those without ascites The levels of conjugated 17 OHCS in the ascitic fluid of one subject who had received intravenous Tetra F rose to a maximum in 6 hours and changed little over the next 17 hours

The results indicate impaired formation of conjugated 17 OHCS after infusion of cortisol but not after infusion of suitable substrates for conjugation i e cortisol metabolites This suggests that liver disease delays the transformation of cortisol to reduced 17 OHCS but glucuronide conjugation of 17 OHCS proceeds readily Perhaps glucuronide conjugation is preserved even in the presence of severe liver disease

(8) J Clin Endocrin 17 1395 1406 December 1957

malities of hormone metabolism in liver disease will eventually be ascribable to the breakdown of specific enzyme reactions —Ed ]

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(7) Gastroenterology 87 129 135 1957

ues of 50 units or less If the history and physical examination are supplemented by determination of alkaline phosphatase GOT and GPT the differential diagnosis of most cases of jaundice can be resolved

► [In the neonatal period normal serum GOT values are up to 120 units and GPT values up to 90 units In hemolytic conditions GOT may increase temporarily but GPT stays normal When jaundice reflects intra or extrahepatic obstruction transaminase values may rise to 800 units (Pediatrics 20 590 1957) —Ed ]

**Effect of Opiates on Activity of Serum Transaminase** was studied in 16 patients by William T Foulk and Gerard A Fleisher [1] Nine had episodes of upper abdominal pain recurring or persisting after cholecystectomy performed 2-40 years before the study Of the other 7 1 had arteriosclerotic vascular disease and hyperlipemia 1 symptomatic esophageal hiatus hernia 1 duodenal ulcer 3 abdominal pain of indeterminate cause and 1 was healthy

Fasting blood samples were drawn for serum amylase lipase and transaminase Codeine phosphate was then given hypodermically *2 gr* and further samples taken 2 4 8 and 24 hours later In most only glutamic oxalacetic transaminase was determined but in 3 patients with postcholecystectomy abdominal pain the glutamic pyruvic transaminase was also measured

In 6 of the 16 patients glutamic oxalacetic transaminase was increased significantly All 6 were among the 9 with postcholecystectomy pain Only 1 had a concomitant increase in serum amylase or lipase following codeine Maximal elevations were approximately 5 10 times the control value and in 1 reached 85 times the control value Serum glutamic pyruvic transaminase showed a parallel rise in the 3 patients in whom it was determined

The mechanism for increase of serum transaminase activity following administration of codeine is not clear but probably changes in the biliary tract or liver related to administration of the opiate are responsible Because of the high transaminase levels found in some patients after codeine caution is indicated in attributing an elevated transaminase level to myocardial infarction or to disease of the liver or biliary tract if a patient has recently received opiates

► [Serum glutamic-oxalacetic transaminase is also said to be increased in the serum in cases of barbiturate poisoning (Acta med scandinav 160 215 1958) —Ed.]

(1) P oc Staff Meet M y Clin. 32 405-410 A g 7 1957

On the other hand although the liver is the principal site of *metabolism of circulating 17 OHCS* other tissues participate and may play a greater role when normal mechanisms are blocked by liver disease

The low maximums of conjugated 17 OHCS achieved by patients with ascites probably reflected the large volumes of distribution rather than a difference in conjugating capacity because conjugated 17 OHCS appear in most extracellular fluids including ascitic fluid

**Significance of Alterations in Serum Enzymes in Differential Diagnosis of Jaundice** Felix Wroblewski[9] (Sloan Kettering Inst ) in studying patients with jaundice whose bilirubin was *2 mg /100 cc* or greater found the serum enzymes

COMPARISON OF RANGES OF SERUM ENZYME ACTIVITIES IN PATIENTS WITH VARIOUS TYPES OF JAUNDICE

| C se | S m Alkali Ph ph tase U it | SGO Tra saminase U it | | SGP Tra saml ase U its |
|---|---|---|---|---|
| E trah pati bilia y tra t b t tl | 8.0-45 0 | 44-288 | < | 64-400 |
| I trah pati prima y d m t stati ca cinoma lymph ma | 8 0-61.6 | 43-300 | > | "6-240 |
| A te l m l g se m d i f ctio h patitis (l cr asi g i t l phase) | 4.0-11 2 | 460-2 140 | < | 600-2,600 |
| Cirrh i | 4 0-15 2 | 45-300 | > | 20-.58 |
| H patot i drug | 3.5-11 4 | 68-3 0 | > | 1 6-440 |
| H moly i | 3 0- 4 3 | 32 140 | > | 29-40 |

Ex lud g bon t t achlor d

capable of distinguishing most types of surgically amendable jaundice from the types best treated medically

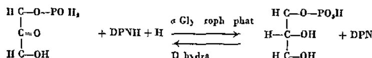
In obstructive jaundice serum alkaline phosphatase is elevated usually above 10 units Serum glutamic pyruvic transaminase (GPT) is increased more than the simultaneously measured serum glutamic oxalacetic transaminase (GOT) The GPT values usually do not exceed 400 and the GOT do not exceed 300 units

*In all types of jaundice amendable by medical* treatment other than that from acute hepatitis GOT values are greater than the simultaneously determined GPT activity In the increasing icteric phase of acute hepatitis the values of GPT are greater than 600 and those of GOT greater than 500 units Transaminase levels in various types of jaundice (table) are to be compared with normal *GOT* values of *40* and *GPT* val

(9) A M A A h I t M d 100 635 641 O t ber 1957

Under conditions of the test normal serum requires over 60 minutes to split fructose 1 phosphate When liver parenchyma is severely injured the value is 3 minutes With decreased injury the time is longer finally reaching the normal value of 60 minutes and over on complete healing The test thus provides quantitative measurement of degree of liver change

In 4 patients with respectively obstructive jaundice chronic cholangiohepatitis with biliary fistula acute cholecystitis superimposed on chronic cholelithiasis with obstructive jaundice and liver metastases the test demonstrated




Fg 94 (C rt y f W lf H P gt l G t t l g 87 17 180 1957)

absence of parenchymal liver damage In 3 patients with slight liver damage fructose 1 phosphate splitting reflected this whereas the enzyme test with fructose 1 6 diphosphate showed normal values With cardiac infarct and muscular dystrophy there is no 1 phosphofructaldolase in serum since the enzyme is not contained in muscle

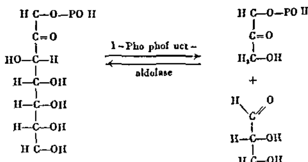
► [The e authors recommend a study of 1 phosphofructaldolase others leucine aminopeptidase (Proc Staff Meet Mayo Clin 32 410 1957) malic dehydrogena e (J A M A 164 647 June 8 1957) and β glucuronidase (Proc Am Gastroenterol A May 1958) It all permits a weak editorial crow of I told you so (1957 58 YEAR BOOK p 597) In this deluge of enzyme tests which apparently is alarming even the originators of the transamina e procedures it is well to remember that the mechanisms of increased enzymatic activity in the blood of patients with liver disease are far from explained and much work will be needed to identify the enzyme test most specific for hepatic damage —Ed ]

**Infectious Hepatitis Studies of Its Natural History and Prevention** were made in about 426 cases occurring among patients and attendants at a state school between 1953 and 1957 Epidemiology effects of gamma globulin and of feeding virus to persons protected by gamma globulin and excretion of virus during the incubation period were studied by Robert Ward Saul Krugman Joan P Giles A Milton Jacobs and Oscar Bodansky[3] (New York)

The disease was sporadic at the school before 1953 40 cases occurred in 1953 47 in 1954 106 in 1955 95 in 1956 and

(3) N w E gl d J M d 8 407 416 F b 7 1958

**Specific Optical Enzyme Test Yielding Information Regarding Parenchymal Damage in Liver** is described by H P Wolf G Forster and F Leuthardt (Univ of Zurich) Along with fructose 1 6 diphosphataldolase used in a test devised by Bruns the liver contains a second aldolase 1 phosphofructaldolase which splits fructose 1 phosphate specifically (see formula in Fig 93) In contrast to the aldolase used by Bruns which is normally present in serum does not split fructose 1 phosphate and is not derived from the liver 1 phos




F g 93 (C u tesy of Wolf H P t l G t t olog a 87 172 180 1957)

phofructaldolase does not appear in serum under normal conditions With cellular damage of the liver especially in acute hepatitis the liver enzyme appears in the serum and splits fructose 1 phosphate In cured hepatitis activity of the enzyme in serum returns practically to nil so the test provides a means of following the healing of hepatitis Even the slightest parenchymal damage is however still recognizable

For demonstration of phosphodioxyacetone formed by fructose 1 phosphate splitting an optical test is used with addition of dihydrocozymase (DPNH) and alpha glycero phosphate dehydrase as catalytic enzyme This carries over the hydrogen of DPNH to the phosphodioxyacetone with formation of alpha glycerophosphate and diphosphopyridine nucleotide (DPN) (see formula in Fig 94)

The process is easily followed in a spectrophotometer because at a wavelength of 340 mμ DPNH has an absorption maximum and DPN is not absorbed The extinction loss is a direct measure of the splitting rate

(2) Gast ent l g a 87 172 180 1957

able jaundice developed 55 days later Of the 5 fed virus alone 4 showed hepatitis with jaundice 39-60 days later

Five months later a challenge feeding of virus was given to 10 patients In none of the 7 previously given gamma globulin and virus did hepatitis with jaundice develop In 1 patient who had previously received virus only and had had hepatitis with jaundice a 2d attack of typical hepatitis with jaundice developed 44 days after the 2d feeding of virus Since only 1 of 4 controls given the challenge dose contracted hepatitis results are not clear cut

The long incubation periods after feeding the virus ranging from 39 71 days suggest that the longest periods were spurious If the true incubation period was about 40 days and if the virus was excreted during the prodromal phase 2 3 weeks after feeding hepatitis which developed at 60 days or longer might repre ent secondary infection To test this hypothesis 10 patients were fed virus and 6 served as controls but lived in intimate contact with the others Three of the patients given virus manifested hepatitis in 39-46 days and 2 more in 60 and 71 days In 4 of the 6 controls hepatitis developed in 60 71 days The controls probably acquired the infection from those fed virus about 3 weeks after the feeding and about 3 weeks before onset of jaundice

Stools which had been excreted by 3 patients on the 25th day after ingesting the virus (2 3 weeks before jaundice appeared) were fed in amounts equivalent to 0 1 Gm to 13 patients newly admitted to the isolation unit Typical hepatitis with jaundice appeared 35 days later in 2 This suggests an alimentary tract phase with multiplication and excretion of virus during the incubation period of infectious hepatitis

► [Two of the ob ervations emphas e the infectivity of viral hepatitis Apparently in the first place o e attack of viral hepatitis does not necessarily confer immun ty although the problem of recrudescense vs reinfection can alway be debated Secondly if virus is excreted in the prodromal phase before the patient ha any ign or symptoms attempts to prevent spread of the disease already difficult because of unrecognized nonicteric cases w ll be most di heartening —Ed ]

**Hemagglutination Reactions Noted in Viral Hepatitis** Blood from patients with infectious mononucleosis agglutinates sheep red corpuscles and this has become a useful diagnostic test Such a hemagglutination principle has been applied to virus hepatitis by testing the reaction of human virus hepatitis serum mixed with red blood cells from sheep dog chicken steer rabbit guinea pig horse and monkey Lester

60 during the first 10 months of 1957 Month to month incidence was similar Age distribution of hepatitis victims was similar to that of other inmates 73 6% being under 20 In 75% onset occurred 6 months or more after admission strongly suggesting that in most cases the disease was acquired at the institution Patients with history of hepatitis were eliminated from the study Gamma globulin 0 01 ml/lb body weight was given intramuscularly to 1 224 patients and 2 988 were left uninoculated During the next 31 weeks 68 patients contracted hepatitis with jaundice 9 (7 4/1 000) had received gamma globulin and 59 (19 7/1 000) had not

In another study of newly admitted and previously uninoculated patients 0 06 ml gamma globulin/lb body weight (6 times the dose of the 1st trial) was given to 1 182 and 1 771 remained uninoculated During the next 39 weeks hepatitis with jaundice occurred in 2 patients (1 7/1 000) given gamma globulin and in 41 (22 5/1 000) controls The larger dose appeared to be more effective although not absolute in preventing the disease

If this effectiveness were due to passive active immunity it might be artificially induced by feeding virus to patients protected by an injection of gamma globulin The stools of 6 patients were collected during the first 8 days of recognized jaundice After detailed preparation the material was fed to newly admitted children aged 5 10 who were brought directly to an isolation unit without contact with the rest of the institution The 1st case of hepatitis with jaundice developed 39 days after administration of 1 ml of the 10% suspension or the equivalent of 0 1 Gm stool Another developed after 71 days A dose of 1 Gm to 11 subjects induced jaundice in 5 and 4 Gm produced jaundice in 12 of 13 Thus the 50% infectivity end point was estimated to be 1 2 Gm

The bromsulfalein retention test was most helpful in patients with equivocal jaundice Serum enzymes phosphohexose isomerase and transaminase values usually increased before the levels in other liver function tests became abnormal

Eleven newly admitted patients were given 0 06 ml gamma globulin/lb body weight and within 30 minutes were fed twice the 50% infectivity dose of virus 5 others received the virus only In 1 of the 11 mild hepatitis and question

were taken after liver function and clinical status appeared *normal following full ambulation*

Intrasplenic pressure was measured in 40 patients and intrahepatic pressure in 17 of these Intrahepatic tissue pressures could not be related to stage or degree of illness size of liver or intrasplenic pressures In 34 the pressure in the spleen was higher at the height of jaundice than during convalescence During the acute phase of the illness 18 had corrected pressure readings above 150 mm water and 7 of these had readings which were 200 mm or over In none of the *patients so examined* were varices demonstrated by esophagoscopy Height of initial pressure could not be correlated with severity of illness degree of jaundice or degree of hepato or splenomegaly In 5 patients final pressure was higher than the measurement taken during the height of jaundice though all the readings were within the normal range below 150 mm water Estimated total hepatic blood flow and splenoportal circulation times were essentially unchanged

Apparently development of acute parenchymal liver injury does not produce severe portal hypertension In acute hepatitis portal pressure is mildly increased

**Plasma Transfusion without Transmission of Serum Hepatitis** Various attempts to free plasma of icterogenic agents have *not been successful Ultraviolet irradiation was a costly* failure Adding chemicals to the plasma is not yet applicable and use of group specific plasma is cumbersome requires direct matching for safety and introduces problems in sterility and clarification Fractionation of plasma wastes albumin and other proteins and is impracticable for blood banks supplying community needs and its cost is a serious problem in centralized blood banks

Paul I Hoxworth and Walter E Haesler Jr [6] (Cincinnati) report a 4 year study (1953 57) in which plasma was prepared from pooled blood of 50 72 donors and stored at room temperatures (72 95 F ) for 6 months before release Bacteria contaminated less than 1% of the plasma human pyrogen tests were negative for all lots and no bacterial disease was transmitted

The plasma pool came from 5 486 donors and was infused into 1 638 patients of whom 556 died early of the original

(6) J A M A 166 1291 1293 M 15 19 8

M Morrison and Robert E Hoyt[4] (Los Angeles) present results of use of red cells of the Macacus rhesus monkey in diagnosing active viral hepatitis

Twofold serial dilutions of the serum of the patient are added to equal volumes of a 2% suspension of red blood cells obtained from a M rhesus The reaction is positive when the cells clump in the fluid medium and cannot be resuspended by gentle agitation

Of 431 patients with miscellaneous diseases 56 gave positive titers of 1 8 to 1 32 Of 22 with acute viral hepatitis either IH or SH strain 19 had significant agglutination titers (over 1 3) and only 3 had titers under 1 8 a positive percentage of 86% Of 14 with chronic viral hepatitis both IH and SH strains 10 (71%) were positive in titers of 1 8 or more Of 9 with acute poliomyelitis 1 was positive in 1 8 titer Of 5 with influenza 2 had titers of 1 8 of 21 with infectious mononucleosis 10 were positive and of 9 with active nonspecific ulcerative colitis 5 were definitely positive It is of particular interest that of 21 patients with jaundice not of viral hepatitis origin all had titers under 1 8 and none was considered positive

The mechanism of hemagglutination is unknown Agglutination may result from the direct action of the virus on the red cells due to action of antibodies against the virus which also acts on the red cells or from presence of some abnormal constituent formed in the course of the disease which has the fortuitous ability to agglutinate the test cells Further studies are indicated to determine whether this test is practical in clinical practice and in screening of blood transfusion donors

► [That the serum of patients with viral hepatitis contains high agglutination titers for Macacus rhesus erythrocytes has been confirmed by Rubin Kemp and Bennett (Science 126 1117 1957) who find the test quite specific and regard the high titers as a direct virus effect —Ed ]

**Splenic Approach to Portal Circulation** Intrasplenic and Intrahepatic Tissue Pressure Measurements in Acute and Convalescent Hepatitis were obtained by Stanley Reichman and William D Davis Jr[5] (U S Naval Hosp Portsmouth Va ) with the patient recumbent Local anesthesia was u ed Patients admitted to the hepatitis ward were studied at the height of jaundice and during convalescence Prothrombin time was above 50% before the test was made Esophagoscopy was done in 23 patients Convalescent measurements

(4) J Lab & Cl M d 49 774 7 8 M y 1957
(5) G troe te l gy 33 609 615 O t be 1957

hemosiderosis in 26 5% and cirrhosis in 2% Steatosis and fibrosis were associated in 33%

Only 1 of the 23 deaths that occurred within 5 days after hospitalization could be attributed to the liver lesion (probable hepatic coma) Several patients had terminal bronchopneumonia but most showed no anatomic cause and death was attributed to cachexia Progress was favorable in 48 of 57 surviving patients

The role of malnutrition in the etiology of hepatic cirrhosis is difficult to establish Morphologic and functional changes are reversible with adequate treatment in most patients but the possibility remains that dietary deficiency of long duration may produce permanent lesions in the liver Fibrosis occurs in over a third of the patients and though this is usually minimal it is possible that in some patients sclerosis could progress to cirrhosis In a study of cirrhotic patients 87% with portal (Laennec s) cirrhosis had a history of dietary deficiency but 83% of them had also prolonged history of alcoholism The authors believe that malnutrition as an isolated factor can produce true cirrhosis but only in a small proportion of cases

► [Although so called liver function tests yielded abnormal results in many patients cirrhosis was discovered in only 1 of 50 malnourished patients subjected to histologic study of the liver and portal hypertension was not evident in any of the 80 cases comprising the whole series The implication is clear it is hard to prove that malnutrition per se without alcoholism leads to cirrhosis in man A similar conclusion was reached by a panel recently discussing hepatic cirrhosis in Washington D C Of roughly a dozen experts from all parts of the world only 1 or 2 thought that malnutrition per se might lead to cirrhosis and none thought the sequence to be common

If malnutrition alone is not responsible for cirrhosis what is either by itself or in conjunction with malnutrition? Viruses? Auto immune reactions? The next abstract clearly implicates a poison and the one after that reawakens the slumbering concept that alcohol may in itself be toxic —Ed ]

**Plants as Etiologic Factor in Veno Occlusive Disease of Liver** were studied by G Bras D M Berry and P Gyorgy[8] with the technical assistance of H V Smith A particular form of infantile cirrhosis in Jamaica is characterized by obliteration of the medium and small sized ramifications of the hepatic veins The ultimate result is a nonportal cirrhosis That a similar lesion developed in a cow in Jamaica lent support to the hypothesis that veno occlusive disease is caused by plant poisons imbibed with bush teas Bush teas

(8) La et 1 960 962 M y 11 1957

disease Of 845 available for follow up 563 were exposed to both plasma (donor population of 5 352) and whole blood (a total of 1 991 units) Jaundice developed in 6 and as no 2 of the 6 received plasma from the same lot the blood was most likely responsible for the jaundice Among 333 who received plasma only from a donor population of 5 157 data were definite in 282 None showed jaundice

Storing plasma at room temperature for 6 months is a practical and effective solution to the plasma hepatitis problem Alteration in albumin is minor and clinical response to stored plasma is the same as to fresh plasma

**Changes in Liver in Malnutrition** were studied by Bernardo Sepulveda Roberto Hernandez de la Portilla Edmundo Rojas and Jose de J Macias[7] (Mexico City) in 54 women and 46 men with primary malnutrition (other diseases and alcoholism were excluded) The patients were aged 18 73 with average age 49 In all diet was generally deficient Intake was under 50% that recommended for normal persons average protein intake was 47% of the normal requirement and animal proteins were reduced to 30% of recommended quantities In most patients duration of dietary deficiency was over 1 year and in a fourth had persisted throughout life

Histologic study of the liver was made in 50 patients (27 biopsies 23 autopsies) The following symptoms and signs of hepatic change were elicited anorexia in 72 2% asthenia in 78 7% edema of the legs in 70% ascites in 21 2% and hepatomegaly in 32% Symptoms were usually mild Icterus was present in 6% and spider telangiectasia in 10% Hemorrhages due to rupture of esophageal vessels were not noted

Liver function tests revealed the following values serum albumin abnormal in 82 5% with average 2 2 Gm /100 cc. total cholesterol abnormal in 67 7% with average 91 mg/ 100 cc cephalin cholesterol flocculation abnormal in 60 3% with average 3+ cholesterol esters abnormal in 50% with average 45% of total bromsulfalein retention abnormal in 42 6% with average 18% prothrombin time abnormal in 42 6% with average 19 seconds compared to a standard of 13 seconds direct serum bilirubin abnormal in 38 5% with average 0 70 mg /100 cc and serum globulins abnormal in 10% with average 4 Gm Histologic studies showed steatosis in 73 6% fibrosis in 35 2% lymphocytic infiltration in 26 5%

(7) R e t cl 9 445 453 Oct D c 1957

These toxins may be unequal in concentration and toxicity and may differ in concentration in various parts of the plants and at various times during the life of the plants

► [The alkaloids of senecio are toxic to the livers of many animals fowl rats and sheep as well as horses and cattle For the most part, however the lesions that have been reported have been those of hepatic necrosis and cirrhosis or occasionally hepatic cancer the striking occlusive vascular lesion shown in the figure has not been particularly noted —Ed ]

**Zinc Metabolism in Hepatic Dysfunction II Correlation of Metabolic Patterns with Biochemical Findings** Glutamic and alcohol dehydrogenase crystallized from liver contain considerable quantities of zinc which is indispensable to the activity of these enzymes Bert L Vallee Warren E C Wacker Anthony F Bartholomay and Frederic L Hoch[9] (Boston) studied zinc metabolism in postalcoholic cirrhosis of the liver

Liver samples were obtained at autopsy and stored frozen until analyzed Two sections each weighing 20 30 Gm were obtained from different parts of the liver Results were compared in specimens from 7 patients with no evidence of liver disease and 5 with histologically confirmed Laennec s cirrhosis Zinc excretion concentration in serum and liver function were studied over a period in 7 patients with postalcoholic cirrhosis All were given zinc orally in physiologic quantities 3 times/day in capsules containing 30 mg zinc sulfate equivalent to a total of 19 5 mg of zinc/day The patients were selected to obtain a cross section of the clinical stages of this disease and each was in a different stage

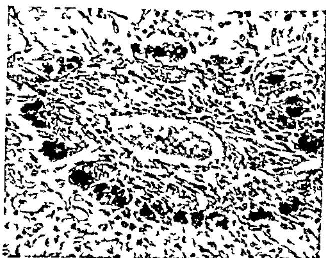
Urinary zinc excretion in normal men was 457 µg /24 hours (S D ± 120) In the cirrhotic patients before zinc was given orally the mean was 1 016 µg /24 hours (S D ± 196) This is the first documented instance of zincuria without albuminuria Oral administration of zinc sulfate to cirrhotic patients with urinary zinc excretion higher than normal significantly decreased zinc excretion and rate of return of urinary zinc excretion to normal levels varied inversely with severity of the disease Urinary excretion decreased from high concentrations in patients with moderately reversible disease to normal in more advanced disease and was extremely low when the process was completely irreversible

In the liver samples taken at autopsy zinc and iron were significantly decreased in cirrhosis With dry weight as a

(9) N w E gl d J M d 257 1055 1065 N 8 19 7

decoctions of the leaves of various plants are taken as a rem edy for diverse ailments Both senecio (ragwort) and crota laria (rattlebox) are regularly consumed by the Jamaican population

Senecio is toxic to horses and cattle and can produce he patic fibrosis and cirrhosis In Barbados crotalaria has been implicated in veno occlusive disease in man is associated with parenchymatous hepatitis in horses and cattle and is



F g 95 —O cl l n n b ch f hepat c ei M ll y trich me sta duced from ×124 (Court y f B as G l l Lancet 1 960 962 M y 11 1957)

toxic to swine chickens quail doves and goats Monocrota line present in crotalaria is a hepatotoxic pyrrolizidine alkaloid

Liver biopsies were done monthly in 5 calves fed on Crota laria fulva Four died without remarkable histopathologic changes in the liver After 6 months the other calf showed an obliterative hepatovenous lesion (Fig 95) All 5 control calves remained free from change during the 8 month ex periment

Hepatocellular damage has been produced with senecio and crotalaria in rats cattle and horses Because of the seem ingly independent and/or concurrent appearance of hepato cellular damage and obliterating vascular lesions more than one toxin may be present each with a different target area

**Production of Tetanus Antitoxin by Patients with Hepatic Cirrhosis** Many injections of equine antitoxin are given each year risking di comfort immediate danger and possible ul timate allergic disease Although it would be preferable to give homologous antibody the level of antitoxin in human serum would need to approach 100 units/ml to make frac tionation into gamma globulin practicable

W Paul Havens Jr Ralph M Myerson and Jean Klatchko[1] (Philadelphia) studied the ability of 28 patients with alcoholic cirrhosis previously completely immunized with tetanus toxoid to respond to a booster dose Their last boost dose of toxoid had been given 10 12 years previously After blood was obtained each was inoculated with 0 5 ml tetanus toxoid and blood then taken at 7 day intervals The amounts of tetanus antitoxin in the serums and ascitic fluid were de termined by titration in mice by injecting appropriate di lutions with standardized doses of tetanus toxin The end point was that mixture of toxin and antitoxin which allowed survival with tetanus on the 7th day after injection

Of the 28 patients 25 had 0 1 or more units of antitoxin/ml serum before the booster dose of toxoid was given In gen eral the amount of circulating antitoxin increased by the 7th day after injection of toxoid reaching a peak in 14 21 days then gradually receding The geometric mean (38 units/ml ) of the maximum response was not remarkable but single large producers of antibody were considerably more frequent than in similarly tested normal persons One had 905 units at the peak of production The patients who pro duced smaller amounts of antibody tended to be in poorer condition with fluid retention and more advanced cirrhosis The 5 patients who produced more than 100 units/ml had no edema or ascites and were in fairly good condition

These data indicate that some patients with chronic he patic disease hyperreact immunologically producing large amounts of antibodies and thus might make excellent sources of tetanus antitoxin However the possibility of transmitting viral hepatitis and the effects of hyperimmu nization and plasmapheresis on patients with hepatic cirrho sis must be considered

► [The capacity of the chronically damaged, or perhaps preferably the chron cally reacting liver to produce ant bodies is here documented Does

(1) New Engl J Med 257 637 643 Oct 3 1957

reference the mean value of 100 μg for the cirrhotic group was 2 standard deviations less than the noncirrhotic mean of 311 μg The data do not indicate whether or not this decrease is due to a change in the chemical composition of liver cells It may simply reflect the replacement of normal liver cells by connective tissue which is low in metal content

All patients had subnormal concentration of zinc in serum and the more severe the liver disease the more marked the decrease The low concentrations in serum zinc were accompanied by significant diminution in the liver content of this element and marked zincuria in patients who had not reached the terminal stages These low zinc contents are most readily explained by a deficiency of zinc which could arise from inadequate intake However the simultaneous zincuria suggests a conditioned deficiency in which normal intake is insufficient because of unusual secondary circumstances Altered liver zinc content an element of crucial significance in oxidative catalysis points to the metalloenzymes as possible loci of biochemical defects The participation of zinc in the dehydrogenation of ethanol and of glutamic acid two substrates that are clearly implicated in the metabolic changes accompanying cirrhosis enhances this view

Perhaps the alcohol dehydrogenase of liver is particularly vulnerable to repeated or continuous metabolic insults by high concentrations of ethanol These episodes could set up a positive feed back system—the higher the dynamic tissue ethanol level the lower the capacity to oxidize it after a threshold had been reached As liver alcohol dehydrogenase seems to bind ethanol in its enzyme action alterations in the protein structure of this enzyme particularly and of other enzymes and tissue proteins might be expected Degradation of bound zinc liberating amino acids and zinc and manifested by the observed aminoaciduria and zincuria could then occur the ultimate result being complete failure of zinc and protein metabolism

► [This is a fascinating demonstration of what may be found with modern analytical technics applied to old diseases On the other hand it may be premature to imply that cirrhosis in the alcoholic develops because the zinc containing alcohol dehydrogenases are overwhelmed Why the administration of zinc sulphate to patients with excessive zincuria should reduce this urinary loss is puzzling the reader may well wonder whether the reduction in urinary loss in the moderately advanced cases was merely an expression of improvement in the hepatic disease —Ed ]

the continuing tissue damage However the elevated antibody titers and hypergammaglobulinemia indicate immunologic hyperreactivity The data favor the concept that certain cases of primary biliary cirrhosis may have autoimmune pathogenesis—the result of antigen antibody reaction occurring in the terminal biliary passages

In this patient thyroidectomy had been performed 3 years earlier and the basal metabolic rate was low The thyroid derivative triiodothyroacetate apparently produced temporary symptomatic remission with fall in serum bilirubin cholesterol and lipid levels but the xanthomas were uninfluenced and circulating complement fixing antibody titers remained elevated

**Xanthomatous Biliary Cirrhosis Following Chlorpromazine with Observations Indicating Overproduction of Cholesterol Hyperprothrombinemia and Development of Portal Hypertension** A case is reported by Jack D Myers Robert E Olson Jessica H Lewis and Thomas J Moran[3] (Univ of Pittsburgh)

Man 31 in January 1955 had acute exacerbation of chronic anxiety and tension He received a total dose of about 3½ Gm chlorpromazine On the 12th hospital day he had fever chills generalized aching and anorexia Icterus and pruritus progressed He became intolerant to fats and had some vomiting Two weeks of cortisone had no effect Five months after onset of jaundice xanthomas first appeared Prednisone and testosterone were without effect Exploratory laparotomy revealed a completely normal extrahepatic biliary tract Biopsy of the liver showed centrolobular changes compatible with chlorpromazine jaundice and numerous granulomatous areas in the lobules and portal areas consisting of large, clear vacuolated cells resembling xanthoma cells Occasional large multinucleated cells of the foreign body type were present

Xanthomas increased greatly first on the hands then spreading to the feet face genitals elbows and knees (Fig 96) In November 1955 the liver was slightly tender and enlarged with a hard edge 10 cm below the right costal margin and an easily palpable left lobe Total serum bilirubin level varied from 9 5 to 11 8 mg /100 ml half the total being direct reacting Thymol turbidity and flocculation te ts and the cephalin cholesterol flocculation test were normal When the plasma was frozen a yellow precipitate turned it opaque This material rose to the surface on centrifugation Total plasma lipid levels were 9 000 mg /100 ml including 4 800 mg phospholipid and 2 500 mg cholesterol/100 ml of which 18% vas esterified Studies of the plasma from the parents showed no evidence for familial hypercholesteremia Coagulation factors assayed in fresh whole plasma

(3) T A Am Phy 70 243 261 1957

it play a role in the perpetuation of the reaction as suggested for chronic hepatitis (1957 58 YEAR BOOK p 575) or for primary biliary cirrhosis as suggested below?—Ed ]

**Primary Biliary Cirrhosis Showing High Titer of Autoantibody Report of Case** The pathogenesis of chronic diseases of the intrahepatic biliary system is unclear A cholangiolar obstructive syndrome or intrahepatic cholestasis may be caused by certain drugs and chemicals such as arsphenamine testosterone and chlorpromazine Primary (xanthomatous or intrahepatic) biliary cirrhosis is a chronic condition rarely preceded by exposure to any agent such as a virus or drug which is known to cause cholangiolar obstruction In most patients no agent can be recognized

Ian R MacKay[2] (Victoria Australia) found circulating complement fixing antibodies in high titer to human tissue antigens in a classic case of primary biliary cirrhosis The complement fixation test was performed with antigens prepared from human tissues obtained within 8 hours of death and from serial dilutions of serum

Woman 38 gradually developed lassitude nausea pruritus and obstructive jaundice several months earlier Laparotomy had shown enlarged lymph nodes in the porta hepatis but no biliary obstruction or disease Liver biopsy showed active chronic biliary cirrhosis She had characteristic findings of jaundice xanthelasmas cutaneous xanthomas heavy lipid deposits in the palmar creases hepatomegaly elevated serum bilirubin level and alkaline phosphatase and gross elevations of serum cholesterol A second laparotomy showed normal extrahepatic biliary system an operative cholangiogram was normal and liver biopsy again showed active chronic biliary cirrhosis

Extremely high complement fixing titers (1 1000) were obtained to a variety of human tissue antigens notably liver and kidney When tested in 7 patients who had biliary obstruction the titers were negative or extremely low

Prednisolone resulted in subjective improvement but no effect was noted on the hepatomegaly or lipid deposits Serum total lipid and cholesterol decreased moderately and complement fixing antibodies decreased transiently

There is a comparable sex incidence of disseminated lupus erythematosus and nonnutritional chronic active hepatitis It is significant that primary biliary cirrhosis also is predominantly a disease of females The significance of circulating antihuman tissue antibodies presumably autoantibodies in disseminated lupus erythematosus and in this single patient with primary biliary cirrhosis is uncertain Such antibodies may be the result rather than the cause of

(2) New England J Med 258 185 188 Jan 23 1958

prothrombin proconvertin and proaccelerin during the xanthomatous phase of the liver disease was unexpected but agrees with the elevation of clotting factors found in 6 of 8 other patients with chlorpromazine jaundice

► [Here documented is a chronic process affecting the intrahepatic biliary system and apparently precipitated by a sensitivity to chlorpromazine The sex of the patient and his recovery also differentiate this case from the typical ca e of primary biliary cirrhosis —Ed ]

**Aldosterone and Antidiuretic Hormone (Adiuretin) in Liver Disease** The role of these hormones in production of ascites and edema in patients with portal cirrhosis was investigated by H P Wolff Kh R Koczorek and E Buchborn[4] (Univ of Munich) Urinary excretion of aldosterone and sodium were determined in 30 normal subjects 10 patients with acute hepatitis 2 with obstructive jaundice 14 with compensated cirrhosis and 16 with decompensated cirrhosis Antidiuretic hormone (ADH) level in the plasma was measured by bioassay in 15 normal subjects 5 patients with acute hepatitis and 10 with compensated and 12 with decompensated cirrhosis In 6 patients plasma ADH activity was checked before and after removal of ascitic fluid

In 2 patients with obstructive jaundice aldosterone and sodium values in the urine were normal In the 14 with compensated cirrhosis in whom salt was moderately restricted aldosterone excretion was normal in some and increased in others whereas sodium excretion was below normal in most In the 16 decompensated cirrhotics accumulating ascites 14 showed high aldosterone excretion and pronounced sodium retention The highest aldosterone and lowest sodium excretions were during acute ascites formation 2 14 days after abdominal paracentesis

When aldosterone excretion of normal subjects and cirrhotics was plotted against the sodium excretion significant negative correlation resulted In acute hepatitis this correlation was noted in only some of the patients Glomerular filtration rate was slightly to moderately reduced but sodium was almost quantitatively reabsorbed in patients with ascites

The plasma ADH level showed no significant difference between normal subjects patients with hepatitis and patients with compensated and decompensated cirrhosis Each group had high normal or low values of antidiuretic activity

(4) A t doc 1 7 45 58 J y 1958

showed remarkably high levels of prothrombin proconvertin and proaccelerin

All manifestations persisted without improvement until Mar 1 1956 13½ months after onset Before this another course of prednisone therapy succeeded only in producing a peptic ulcer which bled briskly Progressive and apparently spontaneous improvement continued from March 1956 and by December 1956 the xanthomas had practically disappeared The liver size decreased and the spleen became easily palpable 6 cm below the left costal margin A third liver biopsy revealed diminished bile plugging and xanthoma cells



F 96—X th m f lbow g on (C rt y f Mye J D *et l* T A Am Phy n 70 243 261 1957)

but fairly extensive hepatic fibrosis particularly in portal areas strongly suggesting biliary cirrhosis Improvement continued and the patient returned to work feeling well

At the height of the xanthomatosis and hyperlipemia the patient had received 8 mg acetate 1 $C^{14}$ The cholesterol pool was many times normal and the absolute turnover rate of cholesterol in grams per day must have been similarly increased In view of the large phospholipid pool in biliary cirrhosis the absolute turnover was also increased In xanthomatous biliary cirrhosis lipid is overproduced because of a change in liver function without any striking pathologic changes in the parenchymatous cells The excess lipid is carried in the plasma by a single abnormal beta lipoprotein of $S_f$11 When it appears high density (alpha) lipoproteins disappear The finding of elevated plasma clotting factors

antidiuretic activity increase in tubular reabsorption of water *and thus in total body fluids Increase in extracellular* volume causes opposite response with decrease in aldosterone and ADH activity renal release of sodium and water and reduction in body fluid volume This pattern is qualitatively the same in normal subjects and in patients with hydropic liver disease

In patients with decompensated cirrhosis however portal hypertension and decreased intravascular colloid osmotic pressure causes ascites The decreased intravascular volume activates the dual retention mechanism to replace intravascular losses of sodium and water and to prevent hypovolemia *The retained sodium and water however fail to reduce al*dosterone activity and to inactivate the retention mechanism because they shift into the peritoneal cavity where they do not affect adrenocortical function This must result in continuous retention of sodium and water with ever increasing ascites accumulation unless the vicious cycle is interrupted by reducing portal hypertension restoring normal osmotic pressure dietary sodium restriction or administration of steroids promoting sodium excretion

**Effect of Amphenone Therapy on Urinary Excretion of Aldosterone and Sodium in Hepatic Cirrhosis with Ascites** *The sodium retaining action of aldosterone probably con*tributes to formation of ascites complicating liver disease Increased amounts of aldosterone are present in the urine of such patients W H J Summerskill and J Crabbe[5] (Harvard Med School) administered amphenone to 4 chronic alcoholics (3 men 1 woman) aged 40 67 with hepatic cirrhosis and ascites and observed the effect on excretion of sodium and aldosterone in the urine Dietary sodium was restricted to 10 mEq daily Body weight abdominal girth *fluid intake and urine output were recorded After* a *period of* equilibration observations were made before during and *after administration of amphenone a total of 11 18 Gm in* 3-4 days Three patients were given prednisone 30 50 mg daily before during and after amphenone to prevent excessive depression of adrenal function and side effects of amphenone Urine was extracted twice—immediately after acidification to pH 1 for free aldosterone and 48 hours later for conjugated aldosterone

(5) La t 2 1091 1095 N 30 1957

among its members In patients in whom ascites developed no relation existed between plasma ADH activity and the degree of fluid retention In plotting plasma ADH activity against serum osmolarity highly significant correlation was found between the antidiuretic activity and the effective osmotic concentration of the serum Removal of ascitic fluid transiently decreased plasma volume and serum osmolarity and increased urinary aldosterone plasma ADH activity and tubular reabsorption of sodium and water After a short transient rise glomerular filtration rate and diuresis decreased and ascitic fluid reaccumulated

Aldosterone and other steroids are metabolized and inactivated by liver tissue Impaired liver function therefore may result in abnormal levels of the hormone in the blood and urine This hypothesis is not compatible with the evidence that excretion of aldosterone adjusts itself by feedback mechanism sensitive to changes in extracellular volume Any increase in aldosterone activity due to deficient steroid metabolism should result in sodium retention and increased extracellular volume This in turn should inhibit further adrenocortical aldosterone secretion until excess circulating aldosterone and retained sodium and water are excreted by the kidneys In patients with cirrhosis and ascites however retention of sodium and water did not reduce aldosterone activity probably because the retained fluid collected in the abdominal cavity and was segregated in a portion of the extracellular compartment in which volume changes are not registered

Water retention in liver disease has been assumed to result from impaired hepatic inactivation of ADH but the present study does not support this view Patients with decompensated liver cirrhosis and normal subjects showed a similar distribution pattern of plasma ADH values After abdominal paracentesis the decrease in plasma volume is accompanied by high ADH activity despite low serum osmolarity Thus during acute changes in plasma volume osmoregulation of ADH activity is suspended

The sequence of events leading to increased extracellular fluid volume are reduction of extracellular volume activation of aldosterone secretion increase in tubular sodium reabsorption increase in body sodium and extracellular tonicity increase in water intake and in posterior pituitary

maintenance steroid with less sodium retaining activity substituted

Man 28 had abdominal swelling in 1955 He had no previous history of liver disease jaundice blood transfusion alcohol ingestion or exposure to hepatotoxin At exploratory laparotomy the liver was tremendously enlarged with a knobby and fine granular appearance Biopsy showed postnecrotic necrosis In the next 5 months he had 8 paracenteses and 1 in each of the following 2 months He received mercurial diuretics acetazoleamide ammonium chloride aminophyl line potassium chloride and ascorbic acid intermittently and varying degrees of weight loss occurred Though the initial diet was to contain 22 mEq sodium daily the patient consumed variable amounts of milk and candy He excreted 70 µg aldosterone in 24 hours markedly above normal Urinary 17 hydroxysteroid excretion was slightly below normal and 17 ketosteroid excretion was definitely low

Between April and June 1956 the patient s condition deteriorated markedly and he required 11 paracenteses in this interval A one stage bilateral adrenalectomy was performed on June 8 1956 He received hydrocortisone hemisuccinate slowly intravenously during the day of surgery From June 18 to 23 while he received 37 5 mg cortisone acetate daily and had only minimal sodium restriction he gained 6 1 g demonstrating a significant sodium retaining capacity On 25 mg and 12 5 mg cortisone acetate daily he gained little weight Sodium excretion was 20 100 mEq considerably higher than preoperative levels When the combination of 12 5 mg cortisone acetate and 5 mg prednisone was given the patient diuresed large amounts of sodium and water and lost weight

This patient demonstrated hyperaldosteronism before surgery Since no hyperplasia of the zona glomerulosa or zona fasciculata was observed decreased hepatic inactivation of the hormone may have been responsible After adrenalectomy urinary excretion of sodium was marked but small doses of cortisone and prednisone were sufficient to maintain the patient perhaps because of the tremendous pool of sodium available in the ascites

After all ascites disappeared the residual defect in sodium metabolism was again apparent since the patient reaccumulated ascites while he was maintained on a liberal sodium diet and 25 mg hydrocortisone daily though no aldosterone was present in the urine The exact nature of the defect is not apparent Perhaps the patient with cirrhosis is more sensitive to glucocorticoids in retaining sodium Undoubtedly extra adrenal factors are also involved in the genesis of the fluid retention in cirrhotic patients

Two patients were emaciated with grossly deranged liver function tests and low serum sodium levels The other 2 had less clinical or biochemical evidence of liver disease their ascites had accumulated suddenly after alcoholic excess Only the latter 2 responded well to mercurial diuretics The 2 severely affected emaciated patients responded to amphenone but also showed toxic reactions to it Anorexia nausea and lethargy developed during the first 48 hours 1 complained of retching in the other diarrhea developed Both had episodes of impending hepatic coma with mental confusion and a flapping tremor

Urinary aldosterone level estimated in 1 severe and 1 mild case of cirrhosis was high and within the range obtained in healthy persons placed suddenly on low sodium diets a large proportion of it being free aldosterone Administration of amphenone produced immediate striking decrease in excretion of aldosterone toward normal levels in both patients An appreciable sodium diuresis occurred during treatment but not immediately related to alterations in excretion of aldosterone

The 2 who had sodium diuresis after bed rest did not respond to amphenone with restriction of sodium intake and mercurial diuretics In the 2 with more severe liver disease in whom routine treatment was ineffective sodium excretion increased from less than 1 mEq to 60 80 mEq /24 hrs in response to depression of adrenocortical function This emphasizes the contribution of adrenocortical hormones to the ascites and suggests that they may be of greatest significance in the intractable ascites of advanced liver disease

► [The trouble with amphenone as shown here and by Wolfe *et al* (New England J Med 257 215 July 25 1957) is that its toxic effects are too pronounced to warrant its use in the routine management of cirrhotic ascites. Ablation of the adrenals as described below also appears rather drastic. The implications however are hopeful a less toxic inhibitor of aldosterone will surely be developed —Ed ]

**Effect of Bilateral Adrenalectomy in Patient with Massive Ascites and Postnecrotic Cirrhosis** A case is reported by Jerome Giuseffi Emile E Werk Jr Paul U Larson Leon Schiff and David W Elliott[6] (Univ of Cincinnati) Sodium retention is a dominant factor in wasting ascites It may be due to high aldosterone activity Thus benefit might accrue if the source of aldosterone could be eliminated and

(6) N w Engla d J Med 257 796 803 Oct 24 1957

overlying the exposed ileal mucosa It is not known whether such secretion of mucus continues after the first 3 weeks

► [The authors of this ingenious operation point out that the muco a of the ileal transplant must continue to function But what about its blood supply? It is implied that the vascular supply of the transplanted segment is left intact but obviously this segment, if it is to bypass a portal block, must establish new vascular connections with the systemic circulation draining the parietes May not the segment should it continue to function secrete material into the ascitic fluid? Finally since digestive enzymes are lacking how is protein of the ascitic fluid absorbed?—Ed ]

**Estimation of Certain Coagulation Factors in Ascitic Fluid Test Characterizing Ascites of Cirrhotic Origin** A G Combrisson J Debray and E Housset[8] (Paris) studied the total proteins paper electrophoretic pattern fibrinogen prothrombin proconvertin and proaccelerin in the blood and ascitic fluid of 39 patients 28 of whom had alcoholic cirrhosis and 11 ascites due to cancer

The total proteins fibrinogen proaccelerin and proconvertin were about the same in patients with cirrhosis as those with tumors Only 9 of the 28 alcoholics showed electrophoretic pattern of beta and gamma globulins suggestive of cirrhosis Four patients with ascites due to cancer showed increased alpha$_2$ globulin In others electrophoresis was of no value in determining the origin of the ascites

Significant results were provided by prothrombin determinations The amount of prothrombin in the ascitic fluid in cirrhosis did not exeed 13% and was usually less (method of Quick) There was no correlation between concentrations in the blood and ascitic fluid In neoplastic ascites prothrombin in ascitic fluid was at least 35% and usually was much higher

Differences in prothrombin level can be useful in the differential diagnosis of cirrhotic and neoplastic ascites although confirmation is needed in a larger series of cases Ascites due to inflammation especially tuberculous peritonitis should also be investigated

The mechanism responsible for the particular behavior of prothrombin in ascitic fluid is a mystery Classically ascites is linked to a disturbance in capillary exchange and why prothrombin passes the capillary filter whereas proaccelerin and proconvertin are present only in small traces in ascitic fluid is not known Apparently this finding does

(8) P m d 65 1 27 12 8 J 29 1957

**Absorption of Ascitic Fluid by Means of Ileoentectropy in Patients with Advanced Cirrhosis** Ileoentectropy was devised to control ascites or hydrocephalus through intestinal mucosa Essential in this procedure is eversion of a segment of ileum within the peritoneal cavity so that the mucosa is bathed by and may absorb ascitic fluid Charles G Neumann George C Adie and J William Hinton[7] (New York Univ) did such surgery in 10 patients who repeatedly accumulated large quantities of ascitic fluid despite prolonged management with sodium restriction diuretics and a high vitamin high protein diet In each the intestinal tract was sterilized by administering a sulfa drug and neomycin None acquired generalized or localized peritonitis indicating that such sterilization was effective

Several methods were used (1) omentectomy then resection of the terminal 15 18 in of ileum entectropy by sectioning the ileal segment along antimesenteric border ileoileostomy then attachment of the serosa of the everted ileal segment to the anterior abdominal wall (2) closure of the stump of the ileum on ileotransverse colostomy and attachment of the everted ileal segment to the right posterior abdominal wall lateral to the cecum and ascending colon (3) section of the segment near the mesenteric attachment and attachment of the serosa of the everted ileal segment to the right posterior abdominal wall lateral to the cecum and ascending colon and (4) removal of the proximal portion of the ascending colon ileoascending colostomy and attachment of the serosa of the everted ileal segment to the right posterior abdominal wall Omentectomy was done in each case to prevent encapsulation of the ileal segment by the omentum Ileotransverse colostomy was instituted to shift the site of anastomosis away from the quadrangle of mesentery going to nourish the everted ileal loop

Of the 10 patients 5 died within 3 weeks of operation and 5 lived In the 4 who could be followed none required further paracentesis though salt has been unrestricted in the interim of 5 weeks 6 months 6 months and 1 year respectively Two patients had about 3 000 cc ascitic fluid The causes of the postoperative deaths were acute hepatic necrosis and massive bleeding from esophageal varices At each of 4 autopsies there was a minimal accumulation of mucus

(7) A n S g 146 700 705 Oct be 1957

subjects may be a valuable early sign of abnormal venous channels The contrast substance may appear to enter the internal vertebral venous plexuses through many dilated intervertebral veins which also receive blood from veins located along the esophagus In no patient was the portal vein




F g 97—M ld port l hype t C t l t se g m eal p m d t rt os ty f t rv rt b l (1) d p t t t l (2) I t l rt b l ple w ll u l d (3) H m 3g g y t m ot w ll d mon t ted ex ept f t m al port f 3g (4) (C u t y f Sch b g R G t ent l g 88 21 31 1957)

or esophageal varices demonstrated by x rays after costal intraosseous venography

In the diagnosis of upper gastrointestinal hemorrhage introduction of a Sengstaken Blakemore tube esophagoscopy barium swallows and splenoportography all have some value and recognized limitations Costal intraosseous venography allows evaluation of the systemic vascular alterations of portal hypertension and is an addition to the present diagnostic armamentarium

not pertain only to ascitic fluid since preliminary studies have shown comparable results in pleural fluid It has also been noted that in certain patients other coagulation factors (antihemophilic factors A or B antilysins) do not pass into the ascitic fluid

► [The differential diagnosis of ascites due to cancer and that due to cirrhosis of the liver is not always easy cancer of the ovary in particular may give trouble Of the 11 patients with neoplasm studied in this report, 5 had cancers of the ovary Let's hope the test proves reliable on further trial —Ed ]

**Costal Intraosseous Venography in Diagnosis of Portal Hypertension** Radiopaque substances introduced directly into ribs normally allow visualization of a fairly constant intrathoracic vascular pattern mainly the intercostal veins corresponding to the site of injection and the azygos system Injection into the 10th rib in the right or left midaxillary line fills the azygos or hemiazygos vein respectively R Schobinger[9] (Buffalo) demonstrated the presence of collateral circulation in patients with portal hypertension

METHOD —The patient is sedated instructed to breathe quietly and lies supine on the x ray table The 10th rib is identified in the left midaxillary line The overlying soft tissues are infiltrated with procaine and a 16 17 gauge bone marrow or spinal needle is introduced into the medulla of the rib Hypaque® 8 10 cc of 50% solution is injected under constant and moderate pressure within 5 seconds One film is exposed during injection of the last 1 2 cc

Normally the contrast substance diffuses only moderately in the medulla rapidly escaping into one or two intercostal veins which communicate with the hemiazygos vein posteriorly In portal hypertension the venous drainage becomes complicated and variations depend on severity of the portal hypertension (Fig 97) An abnormal venous pattern may be present even if esophageal varices are not demonstrable by barium swallow Venous collaterals along the thoracic wall link several intercostal veins Occasionally veins in the anterior abdominal wall (caput medusae) are seen

Evaluation of the x rays suggests that portal blood may be shunted over the vertebral venous plexuses at a relatively early stage of the disease when clinical evidence of portal hypertension may still be lacking The visualization of internal vertebral plexuses with prominent veins connecting with the posterior portion of the intercostal veins in relaxed

(9) G t ent log 88 21 31 1957

revealed only 1 instance in which occlusion had occurred

► [In trying to decide whether to advocate prophylactic shunts in patients with esophageal varices that have never bled Dr Palmer is one of the few sources of data on which we may base our decisions In another article (J A M A 164 746 June 15 1957) he reports that no esophageal bleeding occurred in 21 patients subjected to prophylactic shunting procedures during a 1 4 year follow up period whereas in a control group of 24 12 bled The figure which is needed is this among patients with esophageal varices that have never bled how many will die because of variceal bleeding within 2 3 years? This figure will have to exceed 25% if I am to undertake prophylactic shunts because the mortality of the operation in cirrhotic patients is still between 10 and 15% and in somewhat more than 5% as shown here by Dr Palmer varices may disappear spontaneously —Ed ]

Simple Discriminatory Test for Upper Gastrointestinal Hemorrhage About a third of patients who bleed from the upper gastrointestinal tract bleed from esophageal varices To be able to establish or eliminate this etiology would simplify diagnosis William B McDermott Jr[2] (Harvard Med School) developed a simple qualitative colorimetric test (Fig 98) that can be used by personnel unfamiliar with the quantitative technic The test requires meticulous attention to detail

METHOD —The Conway diffusion dishes and reagents are identical with those used in the quantitative technic The unit should be prepared just before the blood is drawn Twenty drops (0 6 ml ) of boric acid indicator mixture is delivered from a dropping polythene bottle into the inner chamber and 35 drops (1 ml ) of saturated potassium carbonate into the outer chamber The dish cover is sealed with fixative (paraffin and mineral oil) and 3-4 ml venous blood is drawn in a heparinized syringe The dish cover is slid back only enough to accommodate the needle and 1 ml is injected into the outer well The dish is closed a stop watch immediately started and the dish gently rotated about 10 times the two chambers must not be mixed The dish is opened in exactly 3 minutes If the inner chamber remains pinkish or only faintly gray blue the ammonia level is below 120 150 µg /100 ml (normal 40 60 µg ) If the inner chamber turns blue the blood ammonia is above this level and is distinctly abnormal The rapidity and depth of the color development are only roughly quantitative Until the operator is thoroughly familiar with the method a control dish should be used for comparison After use the dishes are washed with soapy water and soaked in 0 1N HCl for at least half an hour thoroughly rinsed dried and stored in a clean jar ready for use

Among 57 patients with no esophageal varices who were bleeding from the upper gastrointestinal tract the blood ammonia level ranged from 20 to 95 µg /100 ml except in one who had a level of 250 µg Among 42 patients bleeding from esophageal varices blood ammonia levels in 41 were

(2) N w E gl d J M d 257 1161 1164 D 12 1957

**Fate of Esophageal Varices in Cirrhosis Following Surgical Portal Decompression.** Eddy D. Palmer[1] (Walter Reed Army Hosp.) followed 63 patients with cirrhosis proved by liver biopsy for 11 weeks to 63 months after surgical portal decompression. End to end portacaval shunt had been made in 49 and end to side splenorenal shunt in 14. Esophagoscopic examinations were made periodically. In 45 controls, shunt had been recommended but had been refused. Esophagoscopic evaluations were made under a 4 diameter magnification. Morphologically the varices were classed as to severity with consideration of both diameter and linear portion of the esophagus over which they extended. Portal venous pressure was measured by transesophagoscopic needle puncture of the varices and direct open manometry, but in only half the follow up examinations were such measurements valid.

STATE OF VARICES AT FINAL EXAMINATION

| [illegible] | Condition of Varices | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| | No. of Patients | | | |
| Portacaval shunt | 34 | 12 | 3 | 0 |
| Splenorenal shunt | 0 | 2 | 10 | 2 |
| Control patients | 3 | 6 | 20 | 16 |

Among patients with portacaval shunt 40% had no demonstrable varices 1 month after surgery. In each patient with splenorenal shunt considerable improvement was noted at the first examination but thereafter successive examinations revealed that 59% showed progressive enlargement of the varices. In time the portal pressure in a few of these patients even exceeded that before the shunt. The results are given in the table.

In the control group unpredictable changes in the varices occurred: in 3 they disappeared temporarily and in 3 others for the entire period of study. After portal decompression varices and portal pressure continue to fluctuate but the pattern is more definite and predictable. After splenorenal shunt conditions become worse in about 6 months, probably because of insufficient communication across the splenocaval pressure gradient. It cannot be explained by thrombosis of the shunt because autopsies in 30 patients with shunts

(1) Gastroenterology 32 861 866 May 1957

revealed only 1 instance in which occlusion had occurred

► [In trying to decide whether to advocate prophylactic shunts in patients with esophageal varices that have never bled Dr Palmer is one of the few sources of data on which we may base our decisions In another article (J A M A 164 746 June 15 1957) he reports that no esophageal bleeding occurred in 21 patients subjected to prophylactic shunting procedures during a 1-4 year follow up period whereas in a control group of 24 12 bled The figure which is needed is this among patients with esophageal varices that have never bled, how many will die because of variceal bleeding within 2 3 years? This figure will have to exceed 25% if I am to undertake prophylactic shunts because the mortality of the operation in cirrhotic patients is still between 10 and 15% and in somewhat more than 5% as shown here by Dr Palmer varices may disappear spontaneously —Ed ]

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(2) New E gl d J M d 257 1161 1164 D 12 1957

Fig 8—D t ls f q al t t te t fo hype ammon ma (C urtesy of McD rmott, W V Jr N w E gland J Med 257 1161 1164 Dec 12 1957)

above 139 µg a level that gives an unequivocally positive qualitative result In 1 the blood ammonia level was normal

A nitrogenous load (blood) in the gastrointestinal tract releases ammonia because of enzyme activity of micro organisms This ammonia is absorbed into the portal circulation but when the portal bed is blocked it bypasses the ornithine cycle in the liver and appears in peripheral blood in abnormal concentrations Thus an elevated blood ammonia

level is not so much an index of liver dysfunction as it is an index to presence of esophageal varices

*An elevated blood ammonia level is not pathognomonic* of bleeding varices A patient may have extensive esophageal varices but bleed massively from some other concomitant lesion into the gastrointestinal tract The blood ammonia level would rise and there would be a false positive test Treatment with antibiotics glutamic acid or arginine before the test negates its value and may result in a fal e negative

► [Only further experience will tell whether this test will prove to be a practical and valuable diagnostic aid In a patient with cirrhosis bleeding massively from a peptic ulcer for example the results may obviously be misleading Finally some reservations may be expressed with respect to the flat footed statement that elevated blood ammonia levels indicate esophageal varices rather than liver dysfunction It would for example hardly explain elevated ammonia levels in a patient suffering from acute hepatic necrosis of a few days duration —Ed ]

Neomycin in Treatment of Hepatic Coma is reported by A M Dawson Janet McLaren and Sheila Sherlock[3] (Postgrad Med School London) Twelve patients with acute hepatic coma and 8 with chronic portal systemic encephalopathy (intermittent stupor) received 4-10 Gm neomycin daily up to 10 months One patient had acute viral hepatitis and 19 had cirrhosis

In 6 who had chronic neuropsychiatric symptoms for 3 months to 3 years uncontrolled by restricting dietary protein to 25 50 Gm daily the flapping tremor disappeared and co-ordination and mental function improved within a week of starting neomycin In 1 patient 3 weeks of therapy were required to attain maximal benefit Improvement persisted in 5 while on neomycin whereas 1 had a relapse after 10 months continuous treatment In 6 of 7 patients with fetor hepaticus the odor disappeared within 3 days of start of neomycin therapy The EEG usually improved but became normal in only 1 The arterial blood ammonium level fell to normal in 7 of 8 patients and then gradually rose to pretreatment levels in 4 during 4 months of neomycin treatment but with recurrence of neuropsychiatric symptoms in only 1 patient

Of the 12 patients in acute hepatic coma 6 improved from deep coma—3 to mild confusion and 3 to normal—and 1 improved from mild coma to normal Two of these 7 continued to bleed and died 12 days later passing into deep coma only

(3) La et 2 1263 1268 Dec 1 1957

a few hours before death 1 died a week later after abdominal paracentesis and 2 died 2 and 4 months later of further gastrointestinal hemorrhage The patient with coma due to acute infectious hepatitis recovered

Stools became bulky pale and usually odorless In 11 patients studied Escherichia coli did not grow after the 2d day and remained absent from the stool cultures for the duration of therapy—10 months in 1 4 months in another and 3 weeks in a third In 2 patients E coli continued to grow and was resistant to neomycin in vitro Another had resistant E coli after a week s treatment Among 4 patients the fecal flora returned to pretreatment findings in all within a week after neomycin therapy had been discontinued Changes in clinical state blood ammonia levels and fetor hepaticus were unrelated to alterations in fecal flora

In 2 patients severe diarrhea began within 6 hours of start of neomycin and stopped within 24 hours of its discontinuance Albuminuria was not noted in any patient receiving neomycin Oral moniliasis developed in 1 but cleared with local treatment while the antibiotic was continued

To test whether purgation could produce the results obtained with neomycin 3 patients were given senna preparation and liquid paraffin to induce stool volume and frequency similar to that induced by neomycin Treatment was stopped in 1 because of nausea vomiting and abdominal cramps Fetor hepaticus persisted in all 3 and the blood ammonia level was unchanged in the 1 tested

► [Similar beneficial results obtained by giving neomycin to patients with liver disease and central nervous system disorders are reported in the American literature (New England J Med 256 1030 May 30 1957 and A M A Arch Int Med 101 467 1958) In general the exhibition of neomycin was attended by a definite improvement in the clinical state and by a fall in blood ammonia levels As might be expected the improvement was often temporary in those with hepatic coma because of an acute episode such as hemorrhage from esophageal varices which often terminated fatally because of the serious underlying condition Those in a chronic state however with mild or episodic cerebral manifestations appeared to be clearly benefited and symptoms were satisfactorily controlled even on a protein intake of approximately 40 Gm a day provided this intake was covered by neomycin

Although a daily dose of 10 Gm appears necessary in some cases others do well on 4 Gm a day Criteria as to dosage required are however most uncertain. As Dawson and his collaborators point out neomycin sometimes appears beneficial even though a continuing effect of the drug on the fecal flora cannot be demonstrated and in a spontaneously fluctuating condition such as hepatic coma evaluation of a single therapeutic maneuver mu t be most cautious —Ed ]

**Effect of l Argınıne on Elevated Blood Ammonıa Levels** ın Man was studıed by John L Fahe) Danıel Nathans and Donald Raırıgh[4] (Natl Inst of Health) Hepatıc or non hepatıc causes may elevate blood ammonıa The lıver may release ammonıa ınto the cırculatıon when certaın amıno acıds e g glycıne are admınıstered parenterally ın the pres ence of relatıve argınıne defıcıency Nonhepatıc sources of ammonıa may be endogenous ın organs other than the lıver such as the kıdney or exogenous e g the gastroıntestınal tract or ammonıum salts gıven ıntravenously

When glycıne alone ıs ınfused ınto fastıng dogs ammonıa ıs released ınto the blood from both lıver and kıdney but mostly from the lıver When l argınıne ıs admınıstered wıth the glycıne the lıver stops releasıng ammonıa and begıns removıng ıt from the blood and the perıpheral blood ammo nıa level falls Apparently when l argınıne ıs adequate am monıa from amıno acıd metabolısm ın the lıver ıs converted to urea and does not dıffuse ınto the blood stream Thus l argınıne dıverts and removes the hepatıc endogenous source of ammonıa and prevents blood ammonıa rıse durıng amıno acıd admınıstratıon

The presence of severe hepatıc dısease correlates better wıth ammonıa concentratıon ın arterıal blood than wıth ıts concentratıon ın venous blood Almost all subjects wıth out lıver ımpaırment showed a negatıve arterıal venous dıf ference ın blood ammonıa ındıcatıng release of a slıght amount of ammonıa from perıpheral tıssues Patıents wıth severe lıver dısease usually had posıtıve arterıal venous dıf ferences ındıcatıng perıpheral removal of ammonıa The arterıal venous dıfference correlates well wıth arterıal blood ammonıa concentratıon

The authors gave l argınıne ıntravenously by a constant ınfusıon pump for 1 2 hours to 8 patıents wıth advanced lıver dısease hepatıc encephalopathy and elevated blood am monıa levels Only 1 was known to have a well developed portal systemıc collateral cırculatıon Inıtıally 5 mM was gıven but subsequently the dose was ıncreased to 140 185 mM (29 5 39 Gm ) wıthout apparent toxıcıty In patıents wıthout lıver dısease blood ammonıa was raısed by ıntra venous ınfusıon of ammonıum cıtrate or ammonıum chlo rıde l Argınıne was then concomıtantly admınıstered ın

(4) Am J M d 23 860 869 Dec mbe 1957

travenously for 1 2 hours at rates equal to or twice that of the ammonium ion

l Arginine produced no change in the clinical status of patients with severe liver disease and only 1 had a significant fall in blood ammonia concentration during the infusion In patients without detectable liver disease intravenous administration of ammonium salts produced a prompt rise in blood ammonia concentration the arterial level becoming higher than the venous level In the 6 patients in whom the blood ammonia level was raised by infusion of ammonia l arginine given concomitantly did not lower these level

Attacking the source of ammonia rather than the site of ammonia removal is more effective when blood ammonia is elevated to levels of clinical significance When the blood ammonia source in man is exogenous clinical usefulness of l arginine is limited

Experiments with Cholecystokinin in Cholecystography Gallbladder contraction and pancreatic enzyme secretion may be caused by substances extracted from the mucous membrane of the upper small intestine In an earlier study Bror Broden (Stockholm) observed the effect of injecting the gallbladder contracting factor cholecystokinin into normal subjects and patients In the normal subjects the contraction of the gallbladder began during the first few minutes after injection of 2 3 mg cholecystokinin and lasted for a maximum of 20 minutes In some partial retrograde filling of the hepatic duct was observed

A second group of 29 subjects presumed to have normal gallbladders were studied after administration of Telepaque* as contrast medium If the diameter of the gallbladder decreased to less than two thirds of the diameter before injection contraction was classified as considerable After injection of 2 3 mg cholecystokinin diluted to a concentration of 1 mg/10 ml in physiologic saline the gallbladder contracted in 26 in 10 of whom the contraction was considerable Contraction usually started as early as 1 minute after the injection and usually took place within the first 10 minutes The duration of contraction occasionally was 30 minutes but usually not more than 20 A second injection of cholecystokinin given 20 minutes after the first usually stimulated a second contraction of the gallbladder

d 1 49 25 9 J y 1958

No severe reaction was observed Seven subjects had slight reactions 2 had a sensation of heat in the face or facial blush 4 had a general sensation of warmth and 1 had pain in the region of the gallbladder The risk of secondary reactions is insignificant if an injection time of 20 30 seconds is used ► [The question Whatever happened to cholecystokinin? is answered in part by this article Although it was nearly dead as far as general medical interest was concerned a group of Swedish and English investigators have been working to purify and isolate this substance first discovered by Ivy At present available cholecystokinin preparations apparently also contain pancreozymin the substance that stimulates secretion of pancreatic enzymes Dr Broden s report, however suggests the likelihood that cholecystokinin preparations in more pure and potent form may become useful tools in the performance of routine cholecystography —Ed ]

**Experimental Production of Gallstones by Incomplete Stricture of Terminal Common Bile Duct** Kamil Imamoglu John F Perry Jr and Owen H Wangensteen[6] (Univ of Minnesota) have frequently found an abnormal degree of narrowing at the terminus of the common duct in patients with cholelithiasis Of 50 patients in whom the sphincter of Oddi was examined 29 had an ampulla too narrow to allow a 3 mm probe to be passed In a postmortem study of 28 patients gallstones were found in 6 and 5 of these had partial obstruction of the biliary tree distal to the site of stone formation Nineteen of the 22 without stones had adequately patent biliary passages

To determine whether gallstones might be produced by a relative stenosis at the ampulla a small strip of cellophane sealing tape dusted lightly with dicetyl sodium phosphate was sutured loosely around the terminal common bile duct just before it penetrated the duodenal wall in the dog rabbit and monkey

At autopsy considerable fibrosis was found in the area of the common bile duct Stones were found in 7 of 8 rabbits in 2 of 8 dogs autopsied 7 20 weeks after operation and in 1 of 2 monkeys One rabbit with complete stricture had stones but all others with complete stricture did not Narrowing but not total obstruction provided the optimal situation for stone development

Stones from 9 animals were analyzed From 2 rabbits they were bilirubin stones and from 4 rabbits 2 dogs and a monkey mixed bilirubin cholesterol concretions Aerobic and anaerobic cultures of the bile from animals with stones were sterile

(6) S ry 42 623 630 O tobe 1957

Apparently partial obstruction to the outflow of bile as might occur with narrowing or fibrosis of the sphincter of Oddi sufficient to provide some stasis yet not enough for manifest icterus may be a cause of biliary stones in man Contrary to previous opinions the anatomic narrowing of the terminal common bile duct is more likely a precursor of gallstones not the result

Operation for gallstones may be incomplete if the biliary papilla is not examined at cholecystectomy This is especially true if the common bile duct is dilated If future studies confirm and establish the sensitivity of the bile duct epithelial component of the biliary papilla to injury by gastric juice surgeons may have to use isolated jejunal loops reattached to the duodenum in the area of the biliary ampulla as a substitute for sphincterotomy

► [It is generally agreed that gallstones may lead to stricture of the biliary ducts and not vice versa. The material here presented points up the inherent weakness of the it is generally agreed traditional bulwark of the weak medical idea On the other hand from the viewpoint of the extent of surgery that may be necessary when operations for gallstones are undertaken the implications of the study are somewhat alarming —Ed.]

**Correlation of Symptoms Age Sex and Habitus with Cholecystographic Findings in 1 000 Consecutive Examinations** was made by C L Hinkel and G A Moller[7] (Danville Pa ) in patients with more or less chronic symptoms who were referred by physicians Each had a fat free supper followed by 3 Gm Telepaque® orally 14 hours before the first x ray Films were made of the gallbladder in prone erect and supine positions When routine films were normal the patient was taken into the fluoroscopy room where erect phototimed pressure spot films were made of the gallbladder with light medium and heavy pressure If the gallbladder shadow was faint or the findings equivocal the patient received 3 Gm Telepaque® and the examination was repeated in 24 hours

X rays were classified as normal or abnormal with such terms as faintly visualized poorly functioning or equivocal being avoided If the concentration of cholecystopaque was insufficient to exclude calculi the examination was repeated If on re examination the shadow was too faint to permit a definite statement about presence or absence of calculi the film was classified as abnormal Most patients were referred for cholecystograms because of excessive

(7) Gastroenterology 32 807 815 May 1957

belching specific food intolerance or right upper quadrant pain Of the 1 000 cholecystograms 343 (34 3%) were classified as abnormal and among the latter opaque or non opaque calculi were revealed in 204 (59%)

Each patient was interviewed by a radiologist before the films were made Excessive belching and gas pains nonspecific right upper quadrant pain and history of jaundice were noted oftener in the normal than in the abnormal group but right upper quadrant colicky pain was 3 times commoner in the abnormal than in the normal group Specific food intolerance (table) was mentioned by 549 patients with fatty

SPECIFIC FOOD INTOLERANCE (COMMONLY MENTIONED FOODS ONLY)

| Type f Food | Freq ency 34 P ls w h Ab rm l Ch l to m | | F eq ency ? P cn th N rmal Ch l to ram | |
|---|---|---|---|---|
| | % | % | % | % |
| G asy fatty f d | 131 | 38 4 | 217 | 33 0 |
| C bb g a d u k t | 23 | 6 7 | 50 | 7 6 |
| I k | 19 | 5 6 | 37 | 6 |
| k w f t | 11 | 3 2 | 8 | 1 2 |
| Choc l te | 9 | 2 6 | 32 | 4 8 |
| A d food t m toe g pef t a d ges | 8 | 2 3 | 3 | 3 |
| O | 7 | 2 0 | 19 | 9 |
| I g t bl sal d | 7 | 2 0 | 19 | 2 9 |
| I | 6 | 1 7 | 19 | 2 9 |
| Gr y | 4 | 1 2 | 8 | 1 2 |
| M lk | 3 | 0 8 | 9 | 1 4 |
| C mbe | 2 | 0 5 | 7 | 1 0 |
| Nut | 1 | 0 3 | 8 | 1 2 |

greasy or fried foods accounting for 348 complaints among the 1 000 patients Since incidence was the same in patients with abnormal and normal cholecystograms no correlation could be established between the symptoms of dyspepsia and cholecystographic findings

As x ray evidence of biliary tract disease was noted in 36% of patients under age 20 in 25% of those aged 30 60 and in almost 50% of those over 60 there appears to be an increased positive yield in young adults and elderly patients The per cent of abnormality was 37 8 in women and 27 1 in men Abnormal cholecystograms were found in 29% of the thin patients 32% of the medium patients and 40% of those having weight ratios over 2 5 Surgery confirmed the abnormal cholecystogram in 99 4% of the patients operated

on Diagnostic accuracy in patients with normal cholecysto grams is undetermined

► [This study should help put to rest the notion that intolerance to fatty foods (meaning epigastric pressure fulness and perhaps nausea after eating such foods) is a symptom of surgically treatable gallbladder disease, i e gallbladders with stones but I am afraid the notion is well nigh indestructible Fat intolerance of the type mentioned (as opposed to biliary colic precipitated by fatty food ingestion) is a symptom more often found in those without than those with gallstones

The view prevailing in most major United States hospitals these days is that gallbladders are normal or abnormal depending on whether or not they contain stones This view however and the division of cholecystographic findings into the two categories of normal and abnormal would strike many European and Latin American physicians as naive. These physicians according to a prominent Brazilian gastroenterologist look on the United States as being in the stone age of gallbladder disease because we ignore functional disorders of biliary tract motility that might cause distress in the absence of stone or inflammation If somebody wants to diagnose a functional disorder of the biliary tract in a patient who has indigestion after a fatty meal I have no objection—he may be right—provided he treats the condition medically Indigestion after a fatty meal by itself should however never be accepted as sufficient indication for cholecystectomy —Ed ]

**Polypoid Mucosal Lesions of Gallbladder** Among 1 331 gallbladders resected at the Ochsner Clinic between 1942 and 1957 G M Carrera and Seymour Fiske Ochsner[8] found 28 with gross polypoid lesions of the cholecystic mucosa 21 of which were discovered during the last 3 years Ten patients also had gallstones and in 2 of these the gallbladder was poorly visualized Only gross lesions were considered The tumors may be single or multiple sessile protrude from the mucosal surface as rounded nodules or pedunculated with stalks of varying thickness The stalk may be so fine that the tumor is readily detached from the gallbladder wall

The types of polypoid mucosal lesions are (1) inflammatory with or without gallstones (2) cholesterol polyps which are normal villi enlarged and infiltrated with cholesterol laden foam cells (3) adenoma a true benign neoplasm (4) adenomyoma usually sessile projecting into the lumen of the gallbladder but also involving the submucosal and muscular layers and (5) carcinoma which may occur in a polypoid lesion In one patient malignant change was observed in fronds of a large pedunculated papillary adenoma

By roentgenography the radiolucent defect is usually small generally 2 3 mm in diameter rarely exceeding 5 mm The shadow is usually rounded with smooth or slightly ir

(8) J A M A 166 888 892 Feb 22 1958

regular edges It maintains a constant position in the gall bladder varying only as the organ is rotated in relation to the x ray beam A tangential study provides a profile view of the lesion which then produces a notch in the outline of the opacified gallbladder (Fig 99) In 2 cases small radiolucent shadows persisted on repeat cholecystograms At operation no lesion was palpated and resection was not done In 3 patients lesions demonstrated by x ray could not



Fig 99—Ad m t g t l w n th ot h p d d g lll d l tl e g l d (C rt y f C G M d O h S F J A M A 166 888 892 F b 22 1958 )

be palpated during exploratory surgery but the gallbladder was resected anyway and in each a small soft adenoma was found Polypoid mucosal tumors are potentially malignant and removal of the gallbladder should be considered unless definitely contraindicated

► [ Polyp has come to be a bad word Although the subject is still highly controversial and pathologic criteria of carcinoma in situ warmly debated (see 1957 58 YEAR BOOK p 567) colonic polyp really means premalignant polyp to many physicians The impetus of the idea has carried it over into the terrain of the gallbladder Thus 3 recent articles either imply or flatly state that polyps of the gallbladder are precancerous although not a single case is presented to support such a conclusion (Am Surgeon 23 1040 1957 Surg Gynec & Obst 105 599 1957 Quart Bull Northwestern Univ M School 31 225 1957) One of these reports concedes

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she was readmitted with another attack During the next 18 months she was readmitted for 4th 5th and 6th attacks She was then re explored Crystal clear yellow green bile and 2 amorphous gray putty like particles were removed from the lower end or the common duct She has been asymptomatic since

CASE 4—Girl 13 months had nausea vomiting and abdominal pain At operation the pancreas was irregular and firm and fat re crosis was pre ent She has remained well

Acute pancreatitis occurs often enough to be considered in the differential diagnosis of abdominal pain and vomiting In the authors cases etiology was unknown but diagnosis of acute pancreatitis was proved by surgery In doubtful cases an elevated concentation of serum amylase is diag nostic Abdominal tenderness may be diffuse but is often centered in the upper abdomen

Of 40 collected cases of pancreatitis in childhood 3 fol lowed trauma 7 were a sociated with ascaris infection of the gastrointestinal tract and 3 with abnormalities of the biliary system Mumps pancreatitis is not infrequent but this in flammation probably does not lead to fat necrosis or pseudo cyst formation When ascaris is the cause pancreatic in flammation appears to result from mechanical blockage of the major pancreatic ducts by the body of the parasite In most cases of acute pancreatitis in children etiology is unl nown

► [Add a nother case of acute and fatal pancreatitis in a 13 year old girl with an ascar s in the duct of Wirsung (Trop Med and Hyg 6 51 1958) —Ed ]

**Pancreatic Necrosis in Cortisone Treated Children** is re ported in 2 cases by H S Baar and O H Wolff[1] (Univ of Birmingham) Necrosis was apparently caused by the cor ticoid therapy The mechanism is unknown

CASE 1—Girl 11 was hospitalized for asthma. Cortisone therapy which had been used previously was started again with 25 mg orally After 5 hours she became deeply cyanotic and dyspneic and died Autopsy revealed a dark red pancreas with darker blackish red spots In the most severely affected areas the secretory cells were anuclear shrunl en pale basophilic and poorly demarcated All intrapancreatic and immediate peripancreatic fat tissue was necrotic

CASE 2—Boy 2 with diagnosis of polymyositis received 25 mg cortisone 3 times/day Ability to breathe and swallow improved Then the condition again began to deteriorate He was discharged on 5 mg prednisolone 3 times/day and the condition remained sta tionary About 5 months later he had abdominal pain vomiting and temperature of 102 F The abdomen was di tended, and a round mass was palpable in the midline below the costal margin A month later he

(1) La t 1 812 815 Ap 0 1957

It has never been conclusively shown that (gallbladder) papillomas are premalignant but the connotation of polyp is too powerful for the authors who conclude Papillomas of the gallbladder should be regarded as premalignant

Claims that gallbladder polyps are premalignant are usually based on a single report that of Tabah and McNeer (Surgery 34 57 1953) who found superficial carcinoma in situ in 3 cases Two of these were found incidentally at operations carried out for biliary tract calculi The third had multiple defects on cholecystography Carrera and Ochsner do not present details of the one case with malignant changes in a gallbladder adenoma mentioned in the preceding abstract

The actual situation is thus as follows (1) No cases have been reported of 1 or 2 small polyps found roentgenologically in an otherwise normal gallbladder which after having been left in place eventually was found to have cancer (2) With the possible exception of the case of Carrera and Ochsner no single polyp in an noncalculous gallbladder has been found to have neoplastic changes even a controversial carcinoma in situ (3) The majority of gallbladder polyps demonstrated by x ray are mucosal projections filled with cholesterol not adenomas or papillomas Under these conditions the finding in an otherwise normal gallbladder of a shadow such as shown in the figure can in no way be considered adequate reason for advocating cholecystectomy —Ed ]

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## PANCREAS

**Acute Pancreatitis in Children** This condition has been sporadically recorded and during the past 50 years 36 cases have been reported in the literature David A Blumenstock James Mithoefer and Thomas V Santulli[9] (New York) report 4 additional cases

CASE 1 —Boy 8 months with no history of illness or trauma was hospitalized for vomiting abdominal pain and shock The pancreas was involved in an acute hemorrhagic process Postoperatively he remained asymptomatic He was in good health at follow up 33 years later

CASE 2 —Boy 6 had abdominal pain and vomiting A gastrointestinal roentgenogram demonstrated distortion of the stomach interpreted as extrinsic pressure from a pseudocyst of the pancreas At laparotomy a large hematoma in the lesser peritoneal cavity was found Recovery was uneventful

CASE 3 —Girl 15 months had sudden peripheral vascular collapse At exploratory celiotomy a perforation was found in the right hepatic duct without evidence of an extruded stone The entire biliary tree was otherwise normal During closure fat necrosis was noted in the round ligament The hepatic duct perforation was thought to be associated with acute pancreatitis She was readmitted 19 months after discharge with abdominal pain and vomiting and after symptomatic treatment for pancreatitis remained well for 10 months when

(9) P d t cs 19 1002 1010 J e 1957

Alterations in Pancreatic Resistance to Bile in Pathogenesis of Acute Pancreatitis In animals it has been impossible to cause bile to regurgitate into the pancreas except with pressures much higher than those which exist in the biliary tree Daniel W Elliott Roger D Williams and Robert M Zollinger[3] (Ohio State Univ ) present experimental evidence that 12 24 hours after obstruction of a common channel a series of events occurs by which bile can regurgitate into the pancreas at physiologic pressures producing pancreatitis

The average pressure in the biliary tree is uniformly lower than the secretory pressure of the pancreas normally and after several hours of obstruction Pressures in the pancreatic duct of one group of dogs were followed for at least 48 hours after obstruction In another group the pancreatic duct was infused with mixtures of bile and pancreatic secretion in varying proportions bile and saline and bile with pancreatic enzymes under physiologic pressure

Following pancreatic duct obstruction there was a uniform rise in pressure over 6-12 hours with peak pressures of 40 80 cm water Within 24 hours of obstruction pancreatic duct pressure fell again approaching the initial normal values of 30 cm water despite continued obstruction of the duct A later secondary rise in duct pressure could not be elicited by food or secretin Obstruction of the common duct increases normal values of 15 20 cm water to 25 30 after 24 hours Therefore common bile duct pressures approach pancreatic duct pressures after 24 hours of obstruction Meantime pancreatic secretions enter the biliary tree and mix with the bile

Infusion mixtures were introduced into the accessory pancreatic duct directly from a manometer at pressures never exceeding 40 cm water When normal bile was infused the pancreas accepted only 2 ml and no significant pancreatitis was found in animals killed 2-4 days later When autogenous bile was diluted with pancreatic secretions from donor dogs somewhat more pancreatic inflammation was observed When bile was incubated with pancreatic secretions and then infused 18-30 ml of the solution flowed readily into the gland under 35 cm water pressure and proved lethal

The effect of bile incubated with saline was no different

(3) A S g 146 669 682 Oct be 1957

had a similar episode and died At autopsy the epigastrium was filled by a firm mass surrounding the pancreas and spleen and attached to the stomach but with no communication with the gastric lumen A plum sized cavity within the mass was filled with diffluent material The pancreas was embedded in the main mass and was hard in some parts and soft in others The tissue was reduced to a few small irregular lobules of pancreas in which secretory cells were intact and contained zymogen granules Most was replaced by necrotic fibrillary or granular debris The peripancreatic fat tissue was necrotic and replaced by irregularly outlined masses of anuclear material

► [Selye reports that cortisol and ACTH tend to aggravate chemically induced pancreatic necrosis in rats (Am J Gastroenterol 29 87 1958) —Ed ]

**Effect of ACTH and Adrenocortical Steroids on External Pancreatic Secretion in Man** was studied by David A Dreiling Henry D Janowitz and Harold Rolbin (Mount Sinai Hosp New York) in 28 patients with no signs or symptoms of pancreatic disease and 31 with proved inflammation of the pancreas After a control period of two 20-minute collections 1 unit/kg secretin was administered intravenously followed by divided collections of gastric and duodenal fluid for 80 minutes Then 40 mg ACTH 100 mg hydrocortisone or 50 mg prednisolone was given intravenously and duodenal drainage collected for 5 hours

None of the 3 steroids stimulated pancreatic secretion On the contrary the rate of flow of bicarbonate secretion and of amylase elaboration appeared to diminish The changes were statistically significant when compared with the average percentage change of basal secretion values in 40 patients not given ACTH or adrenal steroids The decrease was of the same order of magnitude whether or not pancreatic disease was present

Previous investigators have reported pathologic changes in the pancreas of laboratory animals and man and 2 children have died of pancreatic necrosis after long term administration of cortisone and prednisolone The authors study suggests that ACTH and the glucosteroids affect the external pancreatic secretion by depressing it This may be due to pathologic damage to the acinar tissue Therefore use of these drugs in acute pancreatitis is not without danger and until proved otherwise ACTH and the steroids should be limited to those patients with pancreatitis who have evidence of adrenocortical insufficiency

(2) N w E gl d J M d 258 603 605 M 0 1958

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(3) Ann. Surg. 146 669 682 October 1957

than that of freshly diluted bile Thin watery pancreatic juice low in enzymes apparently could not produce the necessary changes in the bile and this mixture was also innocuous However if the donor animal was first fed then stimulated with Urecholine® the secretions were potent suggesting that the change induced in the bile depended on the enzyme content of the pancreatic juice Trypsin was as potent as the most potent pancreatic secretions in inducing the essential change in bile with resulting fatal pancreatitis after infusion Lipase had no such effect Generally the pancreas resisted infiltration by infected solutions

If large quantities of pancreatic secretion are added to less bile the resulting solution enters the pancreas with ease, but pancreatitis is much less severe The pancreas rejects normal bile but accepts its own activated secretions A nearly equal quantity of each is required before the mixture can enter the pancreas at low pressure and for true hemorrhagic pancreatitis to result Bile pancreatitis can vary widely in severity from extremely mild edema to overwhelming necrosis depending on the constituents of the infiltrating solution

The nature of the change in bile on incubation with pancreatic juice is not known After incubation with trypsin or pancreatic juice bile loses its natural opalescence becomes darker and seems less viscous But the change in viscosity is not the determining factor which may be related to the activity of trypsin The data suggest 3 successive steps in the pathogenesis of pancreatitis (1) the entry of pancreatic secretion into the biliary tree (2) incubation of pancreatic secretions with stagnant bile and (3) infiltration of the pancreas at low pressure by this incubated mixture to which it has little resistance

**Ductal and Vascular Factors in Etiology of Experimentally Induced Acute Pancreatitis** were studied in dogs by Rene B Menguy George A Hallenbeck Jesse L Bollman and John H Grindlay[4] (Mayo Clinic and Found ) When the pancreatic ducts were ligated in recently fed dogs innumerable flecks of fat necrosis developed in the pancreas and surrounding tissues In 1 dog histologic findings were typical of interstitial pancreatitis but in all others they were typical of acute pancreatitis with definite parenchymal ne-

(4) A M A A ch. S g 74 881 889 J e 1957

crosis In the 5 dogs tested the plasma amylase level was greatly elevated postoperatively

When the blood supply to the pancreas was impaired the animals remained in relatively good health postoperatively and were hungry the next day There was no spreading pancreatitis and the ducts were normal after ligation of the major pancreatic veins In 7 dogs the pancreatic ducts and major pancreatic veins were simultaneously ligated After operation these animals were extremely ill and 4 were moribund The postoperative plasma amylase level was markedly elevated Innumerable flecks of fat necrosis were noted in the pancreas and surrounding structures and in 3 extended throughout the peritoneal cavity All specimens were grossly hemorrhagic Microscopically all features of acute pancreatitis were present and more marked than in animals with only the ducts ligated When both the major pancreatic arteries and pancreatic ducts were ligated the results were similar but more marked than in either of the two previous groups When the pancreatic ducts were ligated and the left splanchnic nerve then stimulated the degree of pathology was intermediate

The important finding in this study was that obstruction of outflow of pancreatic juice in the face of an actively secreting gland could produce all the gross and microscopic features of acute pancreatitis including pancreatic parenchymal necrosis Previously reported failures to induce acute pancreatitis by this method were perhaps due to the fact that the gland was inactive at the time of the experiments

Autopsies of patients who died of acute pancreatitis rarely show obvious obstruction of the pancreatic ducts such as a stone at the common papilla In such cases one must invoke a spasm of the sphincter of Oddi The pancreatic intraductal pressure is exceedingly susceptible to sudden variations in the tone of the pancreatic sphincter mechanism In man the pancreas is largely a retroperitoneal organ Accumulation of pancreatic juice around the pancreas could conceivably lead to high local tissue pressure which by itself could cause vascular particularly venous stasis Accumulation and concentration of pancreatic juice could lead to blood vessel thrombosis and necrosis When these factors were experimentally produced with duct obstruction degree of pancreatitis was greatly increased

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(4) A M A Arch Su g 74 881 889 J e 1957

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When the blood supply to the pancreas was impaired the animals remained in relatively good health postoperatively and were hungry the next day There was no spreading pancreatitis and the ducts were normal after ligation of the major pancreatic veins In 7 dogs the pancreatic ducts and major pancreatic veins were simultaneously ligated After operation these animals were extremely ill and 4 were moribund The postoperative plasma amylase level was markedly elevated Innumerable flecks of fat necrosis were noted in the pancreas and surrounding structures and in 3 extended throughout the peritoneal cavity All specimens were grossly hemorrhagic Microscopically all features of acute pancreatitis were present and more marked than in animals with only the ducts ligated When both the major pancreatic arteries and pancreatic ducts were ligated the results were similar but more marked than in either of the two previous groups When the pancreatic ducts were ligated and the left splanchnic nerve then stimulated the degree of pathology was intermediate

The important finding in this study was that obstruction of outflow of pancreatic juice in the face of an actively secreting gland could produce all the gross and microscopic features of acute pancreatitis including pancreatic parenchymal necrosis Previously reported failures to induce acute pancreatitis by this method were perhaps due to the fact that the gland was inactive at the time of the experiments

Autopsies of patients who died of acute pancreatitis rarely show obvious obstruction of the pancreatic ducts such as a stone at the common papilla In such cases one must invoke a spasm of the sphincter of Oddi The pancreatic intraductal pressure is exceedingly susceptible to sudden variations in the tone of the pancreatic sphincter mechanism In man the pancreas is largely a retroperitoneal organ Accumulation of pancreatic juice around the pancreas could conceivably lead to high local tissue pressure which by itself could cause vascular particularly venous stasis Accumulation and concentration of pancreatic juice could lead to blood vessel thrombosis and necrosis When these factors were experimentally produced with duct obstruction degree of pancreatitis was greatly increased

than that of freshly diluted bile Thin watery pancreatic juice low in enzymes apparently could not produce the necessary changes in the bile and this mixture was also innocuous However if the donor animal was first fed then stimulated with Urecholine® the secretions were potent suggesting that the change induced in the bile depended on the enzyme content of the pancreatic juice Trypsin was as potent as the most potent pancreatic secretions in inducing the essential change in bile with resulting fatal pancreatitis after infusion Lipase had no such effect Generally the pancreas resisted infiltration by infected solutions

If large quantities of pancreatic secretion are added to less bile the resulting solution enters the pancreas with ease but pancreatitis is much less severe The pancreas rejects normal bile but accepts its own activated secretions A nearly equal quantity of each is required before the mixture can enter the pancreas at low pressure and for true hemorrhagic pancreatitis to result Bile pancreatitis can vary widely in severity from extremely mild edema to overwhelming necrosis depending on the constituents of the infiltrating solution

The nature of the change in bile on incubation with pancreatic juice is not known After incubation with trypsin or pancreatic juice bile loses its natural opalescence becomes darker and seems less viscous But the change in viscosity is not the determining factor which may be related to the activity of trypsin The data suggest 3 successive steps in the pathogenesis of pancreatitis (1) the entry of pancreatic secretion into the biliary tree (2) incubation of pancreatic secretions with stagnant bile and (3) infiltration of the pancreas at low pressure by this incubated mixture to which it has little resistance

**Ductal and Vascular Factors in Etiology of Experimentally Induced Acute Pancreatitis** were studied in dogs by Rene B Menguy George A Hallenbeck Jesse L Bollman and John H Grindlay[4] (Mayo Clinic and Found) When the pancreatic ducts were ligated in recently fed dogs innumerable flecks of fat necrosis developed in the pancreas and surrounding tissues In 1 dog histologic findings were typical of interstitial pancreatitis but in all others they were typical of acute pancreatitis with definite parenchymal ne-

(4) A M A Arch Surg 74 881 889 June 1957

4-7 cm long often oblique from right to left and (3) proximal to this section a sharply bent horizontal portion of regular contour inconsistently visible for 1 3 cm not passing the midline Biopsy in these cases confirmed absence of all histologic change In such instances reflux into the pancreatic duct has no pathologic significance

In group II (44 cases) biliary tract pressures were also normal (8 14 cm of water) but the injected Lipiodol® refluxed easily into a patent duct of Wirsung which seemed to open into the ampulla without evidence of a sphincteric segment Three of the patients had chronic pancreatitis in 8 of 9 others biopsied minimal changes in pancreatic histology were found

In group III (70 cases) biliary hypotony was manifested manometrically by pressures of —3 to +6 cm of water and radiologically by dilatation of the biliary tract Reflux outlined an apparently normal duct of Wirsung not dilated with a duct of Santorini visible in 5 Complete exploration of the pancreas showed abnormalities in 11 confirmed by biopsy in 8 Biopsy in 6 without gross lesions showed pancreatitis in 4 The role of the pancreatic duct reflux in evolution of the pancreatic lesions could not be evaluated

In group IV (89 cases) hypotonia of both the biliary tract and the duct of Wirsung appeared evident In these cases in contrast to the previous groups complete surgical exploration in 77 was negative in only 17 In 60 lesions of chronic pancreatitis were evident usually in the head All 52 cases in which biopsy was done yielded abnormal findings in 46 histologic findings confirmed gross abnormalities

In group V reflux into the duct of Wirsung reflected increased pressure in the region of the ampulla of Vater and was caused by disease of the sphincter of Oddi in 17 and by choledochal lithiasis in 11 other cases Cholangiography showed biliary tract dilatation with partial retention and reflux into the hepatic tree Under pressure the Lipiodol® refluxed into the pancreatic duct for a great distance always passing the angle separating the second and third portions Pancreatic exploration in 57 patients was however positive in only 19 Biopsy confirmed findings in 6

In 13 patients (group VI) the history and surgical findings had indicated chronic recurring noncanalicular pancreatitis in 1 case with calcification Biopsies in 3 confirmed

Animals with the greater degree of pancreatitis had a lower plasma amylase level than did those with less severe pancreatitis probably because of greater destruction of pancreatic secretory tissue This correlates with the clinical impression that the serum amylase level is not always proportional to the severity of pathologic alterations

Local pancreatic vascular disturbances alone either ischemia or venous stasis produced focal or fat necrosis and hemorrhage In no instance was the characteristic gross and microscopic picture of diffuse spreading pancreatitis seen Stimulation of the left splanchnic nerve did not produce acute pancreatitis in the cat or dog

**Reflux of Pancreatic Duct and Pancreatitis Analysis of Second Series of 400 Cases of Cholangiographic Reflux into Canal of Wirsung (1947 56)** is presented by P Mallet Guy and F Giuria The cases represented 18% of all biliary tract operations During operation performed without premedication and under pure ether anesthesia cholangiography was achieved by injecting 2 doses of 10 cc Lipiodol® at a 3 minute interval into the cystic duct or 20 cc into the gallbladder X ray films were taken at several 3 minute intervals following the injections Biliary manometry was also carried out and when indicated histologic studies of the pancreas

Three hundred and forty cases proved suitable for analysis and were grouped according to the pressures in the biliary system the radiologic appearance of the duct of Wirsung and its sphincter and gross and histologic abnormalities in the pancreas and the area of the papilla of Vater The cases included 109 of chronic pancreatitis of which 96 showed a principally pericanalicular reaction and 13 were noncanalicular with diffuse unevenly distributed lesions predominantly left sided

In group I (67 cases) the biliary tract pressure was normal as were cholangiographic x ray patterns with tonic sphincter ready flow into the duodenum and bifurcation of the hepatic ducts well visualized The normal duct of Wirsung showed (1) a sphincteric portion of about 1 mm diameter and 1 cm long with parallel edges descending vertically toward Vater s ampulla at the left of the choledochus sphincter (2) proximal to the sphincter a vertical portion

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(5) Lyon chir 53 481 496 July 1957

strated in patients with reflux into the pancreas and when demonstrated may represent a radiologic artifact These facts argue strongly against the rationale of sphincterotomy in the treatment of chronic or recurrent pancreatitis

► [In all the controversy about the pathogenesis of pancreatitis impaired flow of pancreatic juice appears as a feature common to most postulated mechanisms. As has been seen (page 617) flow may be blocked by a worm and 2 case reports implicate polyps so situated as to obstruct the ampulla of Vater (Ann Surg 145 595 1957 and Brit J Surg 45 394 1958).—Ed.]

Pancreaticoduodenectomy for Chronic Relapsing Pancreatitis Metabolic Defects Created by Total and Subtotal Ablations were studied by Paul H Jordan Jr and Morton I Grossman[6] (Univ of California Los Angeles) in 6 patients (3 total and 3 subtotal pancreaticoduodenectomies) to appraise physiologic alterations that follow such surgery

In 1 patient with subtotal pancreatectomy on a diet of 2 848 calories containing 19 6 Gm nitrogen and 123 Gm fat 11.2 Gm nitrogen appeared in the urine daily and 37% of ingested nitrogen and 29% of ingested fat (34 Gm) appeared in the feces daily When pancreatin (Viokase) was given these values were reduced to 20% of ingested nitrogen and 15% of ingested fat in the stool while 13 Gm nitrogen was found in the urine Absorption of radioiodinated human serum albumin and triolein was normal in 1 patient but abnormal in 2 At operation the remaining pancreas in these 2 patients had appeared grossly abnormal in the former grossly normal In the 2 patients in whom absorption was impaired loss of triolein in the stool was reduced from 35% to 1 5% and of radioiodinated serum albumin from 55 3% to 15.2% after pancreatin was given In subtotal pancreatectomy pancreatic substitution therapy improved the defective absorption but did not restore it to normal

In a patient with total pancreatectomy on a diet of 3 521 calories 24 Gm nitrogen and 129 Gm fat 13 Gm nitrogen was found in the urine 52% of ingested nitrogen in the feces 80 Gm fat in the feces and nitrogen balance was negative When pancreatin was added urine nitrogen rose to 15 7 Gm only 29% of ingested nitrogen and 65 Gm fat appeared in the feces daily and nitrogen balance became positive Fecal calcium was not reduced when fecal fat was reduced by pancreatin and phosphorus balance was negative most of the time In a second patient with total pancrea

(6) A.M.A. A. S. [illegible]

the absence of inflammatory response around the pancreatic ducts The duct of Wirsung appeared normal radiologically or was irregularly deformed Reflux into the duct of Wirsung did not appear to be a causal factor in these lesions

In 40 of the 340 cases some of the films revealed a junction of the bile and pancreatic ducts proximal to the duodenal shadow Since this common channel was most often seen in the first film when the duodenum contained only a small




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amount of Lipiodol® and since it disappeared in subsequent films when the duodenum became increasingly filled with Lipiodol® it is possible that the radiologic appearance of a common channel might have been an artifact Thus the thin radiopaque line between the biliary pancreatic duct junction and the lumen of the relatively collapsed duodenum might have been caused by Lipiodol® lying between two duodenal folds (Fig 100) In 4 cases appearance of a common channel was produced by superimposition of the terminal segments of biliary and pancreatic ducts Of the 40 patients in whom cholangiography suggested a common channel only 10 had pancreatic lesions

These observations indicate that reflux into the duct of Wirsung associated with hypotonia of the sphincter of Oddi and of the sphincter of the pancreatic duct is much more important in the pathogenesis of pancreatic lesions than reflux associated with increased resistance at the sphincter of Oddi A common channel moreover is not frequently demon

strated in patients with reflux into the pancreas and when demonstrated may represent a radiologic artifact These facts argue strongly against the rationale of sphincterotomy in the treatment of chronic or recurrent pancreatitis

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Iron absorption studied by measuring incorporation of $Fe^{59}$ into red cells after oral administration was normal in the 3 patients with total pancreatectomy and 1 with sub total pancreatectomy showed increased iron absorption The influence of the pancreas in regulating iron absorption has been of interest because of the role it may exert on development of hemochromatosis The results suggest that caution is indicated in interpreting increased iron deposits in the liver of animals with inadequate pancreatic acinar function as evidence for increased iron absorption in depancreatized man

In depancreatized patients absorption of oleic acid was superior to absorption of triolein 9% of oleic acid as opposed to 65% of triolein appearing in the stool The oleic acid accumulating in the blood equaled that in normal persons

► [The figures given in the abstract for fecal losses are approximate means of the results of several studies The dose of Viokase was 6 Gm daily —Ed ]

**Evaluation of Biopsy Frozen Section of Ampullary Region and Pancreas Report of 68 Consecutive Patients with biopsy between 1948 and 1955 is presented by Harlan J Spjut and Augusto J Ramos[7] (Washington Univ ) As late as 1951 biopsy of the pancreas was considered generally futile and not worth the risks involved especially because suturing the biopsy wound was difficult and because of the danger of implanting malignant cells should cancer be present

Of the 68 patients 49 had neoplasms—39 carcinomas and 3 islet cell adenomas of the pancreas 6 carcinomas of the ampulla and 1 carcinoma of the common duct—and 19 had nonneoplastic lesions—chronic inflammation and fibrosis pseudocysts 2 abscesses and 1 benign proliferative lesion of the ampullary epithelium

(7) A n. S rg 146 923 930 Decembe 1957

Every frozen section was followed by a permanent paraffin section from the same block of tissue Immediate accuracy of the frozen section was 91% Of the 6 errors all were in patients with cancer and each was an error of underdiagnosis Seventeen patients had radical resections for cancer based on frozen section diagnoses which confirmed the surgical impression of a neoplasm 2 had radical resections for carcinoma even though the frozen sections had erroneously been interpreted as benign

Two patients without and 1 with neoplasm had complications attributable to the biopsy Two of the complications were pancreatic abscesses and 1 was a fistula they appeared 30 8 and 14 days respectively after biopsy Based only on the 49 patients who did not have resection the 3 complications make an incidence of 6 1% The 2 patients with benign lesions of the pancreas both recovered The other with carcinoma of the head of the pancreas died

Among the 68 patients 124 biopsies were submitted for frozen section as many as 6 being done in 1 before satisfactory interpretation was possible On occasion false negative diagnoses were made on several biopsies from the same patient *The drawbacks to biopsy of the pancreas and biliary* tract are (1) prolonged operative procedure and (2) difficulty of interpreting pancreatic lesions Concerning interpretation much depends on the site of biopsy for deep seated lesions in 3 cases needle biopsies of the pancreas proved successful

► [Perhaps biopsy of the pancreas with examination of fro en tissue should be carried out more frequently when the nature of lesions in this organ seems doubtful One important feature of the technic, however deserves emphasis *one* pathologist supervised the entire frozen section procedure and was responsible for interpretation. As is true of so many tests in the gastrointestinal field, whether histologic or biochemical success and effort expended run a parallel course. With an interested individual or an experienced team responsible many diagnostic procedures prove worth while when performed routinely by personnel that happens to be on duty at that time, results are disappointing —Ed.]

Results of Operations of Whipple Type in Pancreaticoduodenal Carcinoma have been compiled by Jonathan E Rhoads Harold A Zintel and John Helwig Jr [8] in experience since 1941 Until May 1952 21 Whipple operations had been done at the hospital of the University of Pennsylvania in 83 patients who had surgery for pancreaticoduodenal carcinoma a resectability rate of 25% Only 17 survived the

(8) Ann S g 146 661-668, Oct ber 1957

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(7) A n. S rg 146 923 930 Dec mbe 1957

# METABOLISM

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PHILIP K BONDY M D

first 30 days but 6 of these are still alive and only 2 have had known recurrence Others are working and leading active lives This rate of 29% is distinctly better than rates obtained in malignancy in some other areas of the alimentary tract Table 1 analyzes the cases by site of origin In

TABLE 1—WHIPPLE OPERATIONS FOR PANCREATICODUODENAL CARCINOMA (UNIV OF PENNSYLVANIA HOSP) ALL PATIENTS OPERATED ON UP TO MAY 1952

| Primary Location | No of Patients | No Surviving 5 Years More | Survivors |
|---|---|---|---|
| Head of pancreas | 6 | 0 | 0% |
| Lower end of common bile duct | 8 | 3 | 37% |
| Papilla of Vater | 4 | 2 | 50% |
| Duodenal wall | 3 | 1 | 33% |
| Total | 21 | 6 | 29% |

TABLE 2—FIVE YEAR SURVIVORS OF WHIPPLE OPERATIONS FOR PANCREATICODUODENAL CARCINOMA FROM LITERATURE

| Author and Year | Head | Ampulla and Papilla | Duodenum | Common Duct | Location Not Stated | Total |
|---|---|---|---|---|---|---|
| Orr T G (collected series) 1952 | 4 | 9 | | | | 13 |
| Dennis and Varco (collected series additional to Orr) 1956 | 8 | 3 | 1 | | 1 | 13 |
| Rhoads Zintel and Helwig 1957 | | 2 | 1 | 3 | | 6 |
| Total | 12 | 14 | 2 | 3 | 1 | 32 |

Table 2 the present series is combined with the recent summary of reported cases by Dennis and Varco

The cardinal symptom of pancreaticoduodenal carcinoma is jaundice usually progressive and not remittent Statistically pain weight loss and various other symptoms may be as frequent but jaundice usually precipitates diagnosis and treatment Radical pancreaticoduodenectomy is worthwhile for the more favorable cases of pancreaticoduodenal carcinoma

► [In view of the discouraging experience of surgeons with respect to the Whipple operation for treating cancer of the pancreatic head the question is often asked how many reported 5 year survivors are there after pancreaticoduodenectomy for cancer of the head of the pancreas? As of May 1957 the answer seems to be 12—Ed ]

# PART VI

# METABOLISM

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## THE PITUITARY GLAND

► ↓ The mechanisms of regulation of anterior pituitary secretion continue to occupy the attention of many investigators Previous work has been summarized in past years (1955 56 YEAR BOOK p 605 1956 57 YEAR BOOK p 617) Separation of the control centers for thyrotropin and gonadotropin seems well documented in the following study —Ed

**Selectivity of Effects of Hypothalamic Lesions on Pituitary Tropic Hormone Secretion in Rat** Hypothalamic lesions in the rat may virtually abolish gonadotropin secretion with testicular atrophy almost as extensive as that after hypophysectomy Atrophy of the adrenal cortex has also been produced and though not eliminating thyrotropin secretion completely thyroid activity has been impaired These effects appear to be selective and a basic question is whether the lesions severally or collectively disrupt specific neural mechanisms concerned with secretion of individual pituitary hormones By means of pituitary bioassays E M Bogdanove[1] (Albany Med College) measured the index of gonadotropin secretion in the pituitaries of rats in which lesions had induced thyrotropic decreases demonstrated by failure of propylthiouracil to cause goiters The hypothalamic lesions were induced by direct current introduced by stereotaxic equipment

Group I (7) showed no evidence of end organ impairment group II (10) showed decrease in thyroid and in testes group III (10) showed goiters as large as in the 17 controls and less severe atrophy of the testes and group IV had atrophy of the thyroid but gonadal function was maintained The adrenal cortices of 2 rats in group IV were atrophic Grossly therefore the rats in group IV would have been considered as demonstrating the selective lesions in the hypothalamus However when bioassays were conducted

(1) E docri l gy 60 689 697 Jun 1957

the ACTH release normally induced by unilateral adrenal ectomy The block most likely was at the nervous system level though the possibility of an effect on the pituitary it self could not be excluded Pitressin® 0 25-0 5 pressor units intravenously caused the release of ACTH in these ani mals Hydrocortisone overdosage induced by injecting 8 mg/100 Gm body weight intraperitoneally also induced suppression of ACTH release and again intravenous Pitres sin® overcame this blockade

In animals with chronic hypothalamic lesions and perma nent diabetes insipidus ACTH release is impaired after *stress but this block is not due to diabetes insipidus per se* Pitressin® could break through this block but the dose re quired was 1 5 units much larger than in overcoming the pharmacologic block Pitocin® epinephrine and histamine were ineffective In rats with acute lesions and transient dia betes insipidus sensitivity to Pitressin® was similar to that in rats anesthetized with Nembutal® morphine and that in *hydrocortisone inhibited rats* Epinephrine was ineffective even when given intraperitoneally and histamine was also ineffective

Rats with acute lesions in the hypothalamus may be the most suitable for testing neurohumoral agents All three types of test animals—acute lesion Nembutal® morphine and hydrocortisone inhibited—respond to a dose of Pitres sin® *only twice that which is effective in the intact rat* Ap parently all three procedures suppress the nonspecific re sponse from this drug and the minimal effective dose 0 25-0 5 units is the dose required to exert an action directly on the pituitary The hypothalamic neurohumor responsible for release of ACTH apparently is not epinephrine hista mine Substance P or oxytocin Results obtained with Pitres sin® protopituitrin and fractions of the chromatogram of Pitressin® indicate a parallelism between vasopressor and ACTH releasing activity The ACTH releasing neurohu mor is probably vasopressin itself

► [*Earlier work by McCann was reported in the 1955 56* YEAR BOOK page 605 The fact that synthetic lysine vasopressin can raise plasma corti costeroid concentration in intact human beings (McDonald Weise and Patrick Proc Soc. Exper Biol & Med. 93 348 1956) suggests that it is truly vasopressin rather than a contaminant which is active In the human *experiments* however since the hypophysis and hypothalamus were intact it remained to be proved that vasopressin is the immediate stimulating agent which works on the pituitary The present studies further support

on the pituitaries only 5 showed extensive impairment of gonadotropin secretion whereas the other 5 were normal. Histologic examination revealed the PAS staining gonadotropes to be as abundant and well stained as those of controls Thyroidectomy cells were present in and acidophilic granulation absent from all anterior lobes studied

All effective lesions in groups II IV were basal and many adhered to the floor of the skull The largest lesions were those in group II which resulted in both goiter block and gonad atrophy with destruction of virtually all the anterior and most of the posterior hypophysis The lesions in group III were smaller than those of group II or were centered more caudally sparing the anterior hypothalamus and destroying a large part or all of the basal periventricular region The lesions of groups IV were generally smaller and more anterior and were centered 0 5 0 75 mm behind the optic chiasm Some extended caudally but they bridged the arcuate nucleus region completely or damaged it less than lesions of groups II and III The 4 lesions which produced adrenal atrophy were among the largest damaging the anterior hypothalamus extensively and extending into the thalamus but a number of seemingly equally extensive lesions failed to produce this effect

The findings are best explained on the basis of selective damage to specific neural mechanisms which support gonadotropin and thyrotropin secretion independently The precise extent of such damage cannot always be evaluated by target organ studies alone More stringent criteria of tropic hormone secretion are necessary before specific neural mechanisms can be identified

**The ACTH Releasing Activity of Extracts of Posterior Lobe of Pituitary in Vivo** The release of ACTH is apparently under neural control by way of the hypothalamus but the precise pathways are not clear There is considerable evidence that release of ACTH is under the control of the antidiuretic hormone liberated from the neurohypophysis S M McCann[2] (Univ of Pennsylvania) reinvestigated the effect of Pitressin® on ACTH release in vivo using rats with ACTH release pharmacologically blocked by Nembutal® morphine anesthesia or hydrocortisone overdosage

Nembutal® morphine anesthesia completely suppressed

(2) E doc nology 60 664 676 M y 1957

in the thyroid available for localizing TSH it may be that the excess of acetylated thyrotropin molecules prevents the localization of unmodified thyrotropin

Acetylation of pituitary preparations with thyrotropic and gonadotropic activity also destroyed the ability to increase uptake of radioactive iodine There was no alteration in the gonadotropic response of chicks treated with a gonadotropic preparation and the acetylated pituitary preparation which indicated that the TSH inhibition is specific

► [Although altered pituitary hormones are not yet available for clinical trial this ingenious idea may in the future lead to important practical developments —Ed.]

**Growth Hormone Content and Metabolic Actions of Human Pituitary Glands** The growth effects of beef and hog pituitary hormones have been studied in rats Besides growth the plasma inorganic phosphate level increases and cardiac and skeletal muscle glycogen is maintained in the fasted hypophysectomized rats However the effects of human growth hormone have never been directly studied and these are now described by Herbert Gershberg[4] (New York Univ )

Pituitaries were removed at autopsy cleaned and frozen *Just before injection the gland was homogenized in 5 20* cc normal saline and then refrozen in 1 cc ampules Test animals were 7 day old postoperative hypophysectomized Sprague Dawley male rats

The results of injection were the same as those produced by purified growth hormone of beef and hog origin growth maintenance of skeletal and cardiac muscle glycogen on fasting and increased plasma inorganic phosphate level Assays of single pituitaries revealed that approximately 100 µg wet pituitary tissue contained 1 growth promoting unit (the daily dose that induces a daily weight increment of 1 Gm in hypophysectomized rats) The growth hormone content of pituitaries from adults over age 45 did not differ significantly from that of a gland from a boy 12 or an 8 month fetus

These observations suggest that cessation of growth in man is not due to a deficiency of growth hormone but to a change in responsiveness of the target cells and that the actions of endogenous growth hormones in animals and man are similar The ineffectiveness of beef and hog growth hor-

(4) Endocrinology 61 160 165 August 1957

the idea that vasopressin itself is the active agent and that it acts when hypothalamic lesions or pharmacologic blockade have rendered other agents impotent An interesting anatomic correlation between the posterior pituitary and adrenocorticotropin has been described by Mialhe Voloss (Acta endocrinol supp 35 1958) who found ACTH in the posterior pituitary of several species and showed that after acute neurotropic trauma (loud noise) the ACTH content of the posterior pituitary falls while that of the anterior pituitary does not change This suggests to Mialhe Voloss that the posterior pituitary might store ACTH for release under direct nervous control just as it is believed to store vasopressin —Ed ]

**Inhibition of Pituitary Hormone Activity with Derivatives of Pituitary Preparations** When thyrotropic hormone is labeled with S³ the preparation localizes in the thyroid but does not increase the weight of the gland Thus the biologic activity of a pituitary tropic hormone (thyroid stimulating hormone TSH) could be dissociated into at least two properties one localizing and the other stimulatory When the labeled preparation was administered with increasing amounts of unmodified TSH less radioactive sulfur became localized in the thyroid gland

On the basis of these observations a theory of inhibitory action was formulated It was assumed that the thyroid contains a limited number of binding sites available for TSH localization If a preparation were available which could not promote growth but which could block the localization of endogenously secreted or exogenously administered TSH such a derivative would be useful as an inhibitor of hormone activity Of 13 derivatives prepared only 3 showed inhibitory properties for thyrotropin These were tested by Martin Sonenberg and William L Money[3] (Sloan Kettering Inst ) in day old cockerels

The dose of unmodified pituitary preparation required to double thyroid weight and triple testes weight was 1 2 5 mg purified or 20 mg crude pituitary extract With a preparation acetylated with acetic anhydride up to 125 mg induced no growth When this preparation was administered with unmodified pituitary preparation the resultant thyroid weight was significantly reduced as compared to the result obtained with unmodified pituitary preparation alone

The acetylated preparations which apparently have lost their stimulatory activity in some cases can still prevent stimulation and presumably localization of the unmodified thyrotropin whether exogenously administered or endogenously produced If there is a limited number of binding sites

(3) E doc I gy 61 12 19 J ly 1957

quate concentrations of adrenal steroids but one able to secrete additional hormone rapidly when stimulated This is in contrast to structural hypopituitarism in which blood adrenal steroid levels are lower and initial response to corticotropin is small

Gonadal failure probably due to gonadotropic insufficiency appears to be the only endocrinologic disturbance in anorexia nervosa

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## THE ADRFNAL CORTEX

► ↓ The manner in which the adrenal steroids exert their actions is not understood but it is clear that more is involved than the quantity of steroid presented to the tissues or the concentration of steroids in the blood (see 1957 58 YEAR BOOK p 615) The importance of the rate of metabolism of the steroids and of the rate of entry into the target cells must also play an important part The next 4 papers consider theoretical and practical implications arising from these considerations —Ed

**Physiologic Disposition of 4 $C^{14}$ Cortisol during Late Pregnancy** Claude J Migeon Jean Bertrand and Patricia E Wall[6] (Johns Hopkins Hosp ) studied the metabolism of radioactive hydrocortisone (cortisol) injected intravenously into women near term The steroid disappeared from the blood only half as fast as in nonpregnant women and less appeared in the plasma and urine as glucuronide derivatives These data suggest that the elevated plasma 17 hydroxycorticoid concentration late in pregnancy reflects a decreased catabolic rate rather than increased secretion

Since cortisol injected into the mother during labor could be found in plasma from cord blood after delivery the steroid crosses the placenta and enters the fetal circulation This may occur with great rapidity since in one instance radioactive cortisol was found in cord blood obtained only 17 minutes after injection of the steroid into the mother Cortisol entering the infant s circulation was excreted rapidly with approximately 80% of the dose appearing in the urine within 36 hours Much of the urine radioactivity was in the form of an unusual and unidentified derivative different from the glucuronide and sulfate excretory products usually found in adults Judging from the amount of radioactive deriva

(6) J Cl I t 36 1350 136 S pt mbe 1957

mone in man is more than likely due to species resistance.

► [For many years it has been believed that the tropic hormones of the pituitary act only on their target glands This implies that ACTH is inactive in the adrenalectomized animal thyroid stimulating hormone is impotent in the thyroidectomized animal etc Recently evidence has accumulated to challenge this idea. Dr F L Engel has brought together the pertinent evidence in an excellent review (Some unexplained metabolic actions of pituitary hormones with a unifying hypothesis concerning their significance Yale J Biol and Med 30 201 1957) Unfortunately the material covered by Dr Engel is too long to be summarized here The review is highly recommended however for those who are interested in the development of modern ideas regarding pituitary hormonal structure and function —Ed ]

► ↓ There would be little justification for including an article dealing with anorexia nervosa in the pituitary chapter, were it not for the persistent claims that this type of chronic starvation is associated with multiple endocrine abnormalities The following article deals with this problem in a more complete fashion than any I have previously seen —Ed

**Endocrinology of Anorexia Nervosa** was studied by Eugene L. Bliss and Claude J Migeon[5] (Univ of Utah) in 5 patients 3 were severely cachectic and 2 though seriously malnourished were not as emaciated

In 2 patients the concentration of gonadotropins in the urine was abnormally low whereas in the third it was in the low normal range This would suggest a gonadotropic deficiency in 2 and a partial deficiency of pituitary tropin in the third patient who had a low normal value associated with scanty menstruation Abnormally small amounts of estrogens were excreted by 2 patients further confirming gonadotropic insufficiency Partial or complete hypophysial gonadotropic insufficiency leading to gonadal failure has also been observed in malnourished experimental animals as well as in patients with a true anterior pituitary failure

The protein bound iodine levels in the serum of 3 patients and the butanol extractable iodine level in a fourth subject were normal Thyroidal $I^{131}$ uptake at 24 hours was normal in 2 patients In anorexia nervosa apparently the thyroid gland is functionally normal since the results of specific tests of its activity are normal and histologic changes at autopsy are minimal

In 4 patients the titer of circulating adrenal steroids in the blood was in the high normal range Intravenous administration of corticotropin (ACTH) promoted a normally prompt increase in these levels Such observations indicate not only an adrenal gland supplying the tissues with ade

(5) J Clin E doc n l. 17 766-776 J 1957

normalities in disposal of hormones may be the cause of some syndromes now called idiopathic

► [The pharmacodynamics of newly described steroid derivatives may also depend on the rate of metabolism as indicated below —Ed ]

**Relation between Biologic Activity of Hydrocortisone Analogues and Their Rates of Inactivation by Rat Liver Enzyme Systems** Desaturation of the 1 2 position and introduction of substituents on the 2 6 and 9 carbons have increased the biologic activity of hydrocortisone It has been suggested that this is due to a decrease in the rate of its metabolism by the tissues To test this hypothesis E Myles Glenn R O Stafford S C Lyster and B J Bowman[8] (Kalamazoo Mich ) incubated various steroid compounds with rat liver slices and compared the rate of their metabolism to the inactive reduced form with their potency in depositing glycogen in the adrenalectomized rat

The rate of reduction of the C 20 ketone was faster than that of the $\Delta^4$ 3 ketone $\Delta^1$ hydrocortisone and $\Delta^1$ 9α fluoro hydrocortisone (3 and 42 times as potent as hydrocortisone respectively in glycogen deposition) were metabolized at correspondingly slower rates by liver slices A new derivative $\Delta^1$ 6α methylhydrocortisone 8 10 times as potent as hydrocortisone in glycogen deposition disappeared at a correspondingly slower rate in vitro

These data show that introduction of substituents on the molecule slows the rate of reduction of the steroid to the inactive tetrahydro or C 20 alcohol forms Increased biologic activity indicated by liver glycogen deposition is apparently closely related to the increased resistance of these analogues to enzymatic attack by the liver When reduction rates are correlated with potency ratios an almost straight line relation is found (Fig 101)

Some hydrocortisone analogues which are inactive as glucocorticoids (2α ethyl 2 methylene 6β fluoro and 19 nor hydrocortisone) do not show this simple relation One possible explanation for the inactivity of 2α methylcortisone as a glucocorticoid is the relative inability of rat liver enzyme systems to convert this compound to the corresponding 11β hydroxylated derivative

These studies indicate that the liver plays a significant role in regulating the degree and duration of biologic response to a steroid hormone Future experiments must deter

(8) E doc logy 61 1 8 142 A g t 1957

tives excreted by the infants about 2 3% of the cortisol injected into the mother entered the fetus

► [Women with adrenal insufficiency tolerate pregnancy well and often need less steroids for maintenance than in their nonpregnant state The previous paper explains in part the greater physiologic efficiency of a given dose of steroids in pregnant women A comparable increase in the effectiveness of cortisone may occur when the rate of metabolism is slowed for other reasons The following paper reports such a situation—Ed.]

**Cushing s Syndrome Produced by Normal Replacement Doses of Cortisone in Patient with Defective Mechanism for Steroid Degradation** Endocrine disorders are usually considered in terms of over or underproduction of a hormone or as iatrogenic due to excessive quantities of one or more compounds Seldom is the possibility considered of disorders in the mechanisms of destruction inactivation or excretion of a hormone John Eager Howard and Claude J Migeon[7] (Johns Hopkins Univ ) report a case which they consider an example of this type of disturbance

Man 43 had hypophysial surgery for acromegaly 5 years previously followed 3 years later by classic panhypopituitarism Steroid assays were low and the glucose tolerance curve was flat At that time he had a 1 1 albumin globulin ratio and a 4+ cephalin flocculation reaction He was started on 30 mg methyltestosterone daily and 25 mg cortisone orally in divided doses which resulted in dramatic improvement After 2 years of treatment he complained of severe morning headaches He weighed 200 lb and the face and neck were fat but the arms and legs thin Striae were broad and red over the abdomen. Blood pressure was 210/115 Results of the tests were abnormal and the albumin globulin ratio was 1 1 The protein bound iodine level was 1 3 µg /100 ml and rose to 2 8 µg after 3 daily injections of thyroid stimulating hormone With the addition of 2 gr thyroid daily he lost weight appetite decreased and blood pressure fell to 150/90 The protein bound iodine level became 6 1 µg

Intravenous hydrocortisone 1 mg /kg body weight given over a half hour period demonstrated impaired degradation Abnormal amounts of hydrocortisone were detected over 6 hours When the hypothyroidism was corrected the degradation curves returned toward but not to normal

Corticoids are degraded slowly in hypothyroid states and in hepatic cirrhosis Both these conditions were present in this patient

In evaluating syndromes due to excessive quantities of a normal hormone the possibility of impaired disposal must be considered In such cases normal production of a hormone or administration of normal amounts may become physiologically excessive Perhaps enzymatic or other ab

(7) Am J M Sc 235 387 393 Ap 1 1958

was present in 5 2 showed weight loss 2 hypoglycemia and 4 water and electrolyte disturbances Severity of symptoms varied widely and could not be correlated with levels of urinary 17 hydroxycorticosteroids Control levels were within normal limits 1 10 mg/24 hours The diurnal pattern of excretion was normal in 2

In all 7 25 units of ACTH intravenously over 8 hours on 2 or more consecutive days failed to elicit the rise in 17 hydroxycorticosteroid excretion which would be expected from a normal adrenal gland although a small initial rise in excretion was noted in 3 Urinary 17 ketosteroid excretion was also normal and did not rise after ACTH administration *The eosinophil count did not fall as it normally does* after administration of ACTH Chromatographic analysis of the urine showed the responsible compound to be tetrahydrocortisone a major metabolite of hydrocortisone

*Final diagnosis of complete adrenocortical insufficiency* rests on absence of adrenal steroid metabolites in the urine Once this is established response to ACTH differentiates secondary from primary adrenal insufficiency In the former the defect is at the adrenal level and prolonged administration of ACTH fails to elicit a rise in urinary corticoids In the latter prolonged administration of ACTH gradually increases corticoid excretion Partial adrenocortical insufficiency likewise depends on evaluating the response to ACTH Lack of urinary 17 hydroxycorticoid response after maximal stimulation with ACTH despite normal control values is the criterion for such a diagnosis

In the 7 patients adrenocortical insufficiency was partial or compensated Secretion was sufficient to maintain homeostasis under resting conditions but evidence of insufficiency appeared under conditions of stress Early clinical recognition of partial adrenocortical insufficiency is of practical importance because under conditions of severe stress acute adrenal insufficiency may occur and go unrecognized

► [How is it possible for a person who has a normal plasma cortisol concentration (Christy J Clin Invest 34 899 1955 Eik Nes J Clin Endocrinol 15 13 1955) and who is excreting normal quantities of steroids in his urine *as described above to have the clinical signs of Addison's disease*? Why should such individuals have pigmentation of their skin low blood pressure weakness disturbed electroencephalograms (Skanse Acta endocrinol 27 469 1958) *etc. at times when the amount of steroid available appears to be normal*? It is not easy to explain this paradox away by saying that their adrenals cannot respond to stress in a normal fashion even

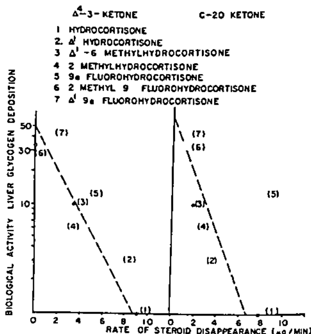


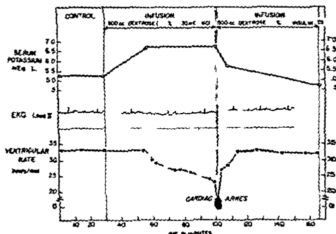

Fig 101 —C l t on betw n b olog c act ity (l er glyc ge d pos t n) a d d ppea te of t d alo t l m som s per t t f t s. (Courtesy of Glenn E M et al Endocr l gy 61 128 142 August 1957)

mine the extent to which various processes such as disease and alterations of the internal and external environments modify the ability of the liver to affect changes on the steroid molecule

**Adrenocortical Insufficiency with Normal Basal Levels of Urinary 17 Hydroxycorticoids Diagnostic Implications** Najib Abu Haydar Jacques R St Marc William J Reddy John C Laidlaw and George W Thorn[9] (Boston) observed 7 patients with some stigmas of Addison s disease but with normal basal levels of 17 hydroxycorticoid excretion in the urine They failed to respond to ACTH with a rise in steroid excretion demonstrating no significant adrenocortical reserve

In 6 patients the first symptom was hyperpigmentation most prominent in exposed areas extensor surfaces pressure points skin folds scars and mucous membranes Weakness

(9) J Cl n E docr L 18 121 133 F br y 1958.




F 10 —Effect f inf on f pota m on entricula rate. D g f ion f 30 mEq potas um blood 500 cc se um pota si m se to 6.6 mEq/L. but ent cula te p g ess ly l wed. C d c est d loped j t bef e nd f i f on Cont l ent cula te was rap dly tored afte dmn trat on f glucose d n ul n. Ar w show x t t me t wh h t cing wer taken (Court sy f Hudson J B et l New England J M d. 25 5 9 536 S pt. 19 1957 )

mineralocorticoid, the patient was started on 0 125 mg 9α fluorohydrocortisone acetate each day and allowed a normal diet excluding only salt added at the table and certain foods high in potassium This do e of steroid has much greater effect on electrolyte excretion than on intermediary metabolism The patient had no further difficulty during 1 year of follow up

**Pattern and Significance of Aldosterone Excretion by Postoperative Surgical Patient** were studied by James H Casey Earl Y Bickel and Bernard Zimmermann (Univ of Minnesota) The characteristic response to surgery in organic metabolism is a catabolic reaction involving increased nitrogen excretion and decreased glucose tolerance associated with fall in circulating blood eosinophils and increase in blood and urinary 11 oxy 17 hydroxysteroids of adrenal origin This is the response of the adrenal cortex to pituitary corticotropic hormone The pituitary in turn is probably responding to certain centers in the hypothalamus

The changes in inorganic metabolism are also mediated through the adrenal but are subject to different mechanisms Aldosterone the potent sodium retaining adrenal hormone is apparently produced in the zona glomerulosa It is present

(2) S g Gy ec & Obst. 105 179 185 A gust, 1957

though this is true (1954 55 YEAR BOOK p 611) In any case the diagnosis of Addison s disease cannot be discarded simply because basal plasma or urinary steroid levels are normal some sort of provocative test is needed. —Ed ]

**Hypoaldosteronism Clinical Study of Patient with Isolated Adrenal Mineralocorticoid Deficiency Resulting in Hyperkalemia and Stokes Adams Attacks** Most patients with Addison s disease have sodium depletion and hyperpotassemia with associated deficiency in glucocorticoid hormones particularly hydrocortisone Spontaneous potassium intoxication is unusual James B Hudson Aram V Chobanian and Arnold S Relman[1] (Boston Univ ) report a patient with chronic complete heart block in whom Stoke Adams attacks developed that were entirely ascribable to hyperpotassemia which was due to relatively isolated deficiency in adrenal mineralocorticoid production It was considered pure hypoaldosteronism

Man 71 had dyspnea for 1 week On examination he had blood pressure of 180/80 and regular pulse rate of 32/minute with signs of congestive heart failure Serum sodium was 137 potassium 5 chloride 107 and carbon dioxide 27 mEq /L ECG revealed complete heart block He improved on low sodium diet digitalis and mercurial injections On the 7th day he suddenly had convulsions coincident with drop in pulse rate to 10/minute Serum potassium at this time was 6 8 mEq but the next day when the pulse rate was 32 serum potassium was 5 2 mEq /L Five further episodes of cardiac slowing requiring use of an external cardiac pacemaker were associated with serum potassium values of 6 3 8 9 mEq /L Intravenous drip of 500 cc of 2 5% glucose in water containing 30 mEq potassium chloride induced gradual fall in ventricular rate (Fig 102) as the serum potassium level rose until cardiac arrest supervened Cardiac arrest was reversed by the external cardiac pacemaker and rapid infusion of glucose and insulin mixture This experiment strongly suggested that hyperkalemia was the cause and not simply the result of the changes in cardiac rate

The kidneys responded to desoxycorticosterone acetate by increasing clearance of potassium and sharply reducing sodium excretion which indicated this was not primarily a renal disorder An 8-hour intravenous ACTH test reduced circulating eosinophils from 88 to zero the water diuresis test was negative insulin and glucose tolerance tests were normal and ketosteroid and oxysteroid excretion were normal suggesting that the adrenal gland was capable of responding normally to pituitary stimulation

Simultaneous studies of the urine in 3 laboratories indicated a defect in aldosterone excretion On normal sodium intake aldosterone excretion was undetectable and response to low sodium diet was grossly inadequate In view of this apparently isolated deficiency in

(1) New England J Med 257 5 9 536 S £1 19 195

centers in the central nervous system would seem by exclusion to be the most important underlying mechanism The exact location of these centers is unknown but they presumably control salt regulating functions of the adrenal through a humoral mechanism Under circumstances of trauma these centers may be directly stimulated to release their tropic hormone through afferent nerve impulses from the periphery

► [Although aldosterone excretion is increased after surgery part of the sodium retention which occurs postoperatively may reflect some other process in which aldosterone participates only in a permissive role as shown by Rosenbaum (1956 57 YEAR BOOK p 630) —Ed ]

**Malignant Hypertension with Increased Secretion of Aldosterone and Depletion of Potassium** is reported by C Holten and V Posborg Petersen[3] (Univ of Aarhus) Increased urinary secretion of aldosterone has been classified as primary if caused by an abnormality of the adrenal cortex and secondary if the abnormality arose outside the adrenal gland and no specific features were ascribable to aldosterone

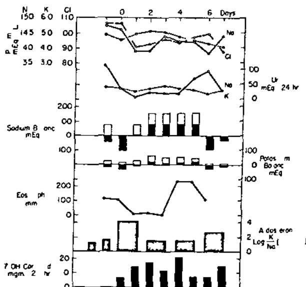
Girl 13 with short illness of fever and rash 1 month previously had intermittent abdominal pain occasional vomiting and fatigue During 6 weeks of hospitalization she had slight fever but all laboratory tests and examinations were normal Subsequently she had repeated generalized convulsions but between seizures neurologic examination was normal Blood pressure was variously recorded as 160/120 170/110 and 120/90 Ophthalmologic examination revealed mild papilledema and hypertensive vascular changes which increased to 5 D During the 6 months of illness weight had decreased from 43 to 32 kg

The urine was either alkaline or neutral and contained 2 Gm protein/L The sediment contained 1 2 red blood cells and 3-4 white blood cells/high power field specific gravity 1 006 Blood urea nitrogen was 11 mg /100 ml plasma carbon dioxide 32 chloride 89 sodium 125 and potassium 2 9 mEq /L uncorrected by oral supplements of sodium and potassium The 24-hour excretion of adrenaline and noradrenaline was normal and blood pressure did not fall after phentolamine intravenously Excretion of corticoids was elevated of 17 ketosteroids and 17 ketogenic steroids normal Excretion of aldosterone was increased to 38 μg in 24 hours and that of free hydrocortisone was 72 μg Tomography after presacral air injection suggested enlargement of the left adrenal gland

On exploration both adrenals were normal The left adrenal was removed and histologic examination was normal The blood pressure did not fall and the papilledema remained at 5 D Need for antihypertensive medication was urgent and pentolinium therapy was begun. Blood pressure fell quickly from 200/140 to 150/90 retinal lesions regressed papilledema disappeared completely ECG re

(3) Lancet 2 918 92 Nov 3 1956

in normal urine and in the urine of patients with hypophysectomy and panhypopituitarism and its output is strongly increased when sodium intake is low It is largely independent of the pituitary Aldosterone excretion was consistently elevated for 24 hours following surgery but in most patients persisted no longer than 2 days returning to normal long before the balance of sodium ion reached equilibrium (Fig 103) and there was little correlation between




F g 103—C f lect lyt and ry st d p t ent f ll w g s bt tal c lect my In eco d g sod m d pot m b la s tak s ch t d pw d f om e l O tp t b rt d d w wa d f m top f take bar Am t f po t e or n gat e balan d ff ence betwe np t a d tput d d ted by h ded one. P t nd eg t e bal s a th f ec d d by h d d ea abo and bel w er I n pect ly (Court y of Cas y J H *et al* S g Gynec & Ob t. 105 179 185 August 1957)

aldosterone output and plasma concentration of sodium or other ions Maximum aldosterone levels were rarely more than twice the preoperative level whereas urinary 17 hydroxycorticoids increased fivefold

These findings make it unlikely that aldosterone can be responsible for the sustained sodium retention which follows surgery Aldosterone excretion showed no correlation with the extracellular sodium or potassium concentration indicating that neither this nor extracellular fluid volume could be the regulating mechanism Direct stimulation of

tity By the 9th day of sodium depletion adrenals from experimental rats secreted progressively larger quantities of aldosterone and lesser quantities of corticosterone Aldosterone is normally synthesized by the rat adrenal in small amount and secretion of other steroids including corticosterone is much greater As a result of sodium depletion the ratio of aldosterone to corticosterone secretion is changed with larger quantities of aldosterone being produced The rate of aldosterone secretion by the rat adrenal can vary independently from that of other hormones

*Correlation of histologic changes with steroid hormone secretion*—Hypertrophy and alterations in lipid content of the zona glomerulosa of the adrenal cortex have been demonstrated in the adrenal cortex of rats fed a sodium deficient diet The authors found that the gross and histologic appearance of the adrenal cortex of control rats remained unchanged throughout the test except for increase in total width as the rats grew Characteristically the zona glomerulosa contained abundant lipid droplets and was demarcated from the deeper cortex by a prominent lipid free transition zone The zona fasciculata also contained lipid the heaviest deposits being in the outer portion

The adrenal cortex of sodium deficient rats underwent progressive changes The zona glomerulosa enlarged by the 2d day and continued to increase in width becoming 8 times wider than in control rats after 2 months of sodium deficiency During the 1st week lipid accumulated in greater amounts but was still stored in the usual droplet form (Fig 104 *A*) After 2 weeks large globules appeared in the outer portion (*B*) After 1 month almost all lipid was in the form of globules After 2 months large lipid globules were noted throughout the entire width of the hypertrophied zona glomerulosa After 1 2 weeks of sodium depletion the zona fasciculata became narrow and depleted of lipid (*B*) and by 2 months could not be distinguished from the transition zone Enlargement of the zona glomerulosa was due to hypertrophy of individual cells and increase in number of cells

Accompanying steroid studies indicated that the zona glomerulosa was secreting faster in sodium deficient rats than in pair fed controls Production of steroids was also increased for otherwise the cells would have been depleted of lipid Thus the zona glomerulosa becomes hyperactive

turned to normal serum levels of sodium and potassium became normal plasma carbon dioxide fell and serum chloride rose to normal polyuria subsided specific gravity of urine increased and proteinuria decreased to 0 3 0 4 Gm /L Clinical improvement was striking Weight increased to 46 kg in 5 months Excretion of reducing corticoids aldosterone hydrocortisone was normal

The patient had hypertension muscular weakness paresthesia tetany thirst and polyuria The urine was alkaline and of low specific gravity and contained protein Hypokalemia and alkalosis persisted A large intake of potassium was followed by a slow rise in serum potassium level and increased renal excretion All these findings are features of primary aldosteronism The outstanding differences were the rapidly developing malignant hypertension absence of morphologic abnormalities in the adrenal cortex and presence of hyponatremia

**Alterations in Rat Adrenal Cortex Induced by Sodium Deficiency** were studied by Albert B Eisenstein and Phyllis Merritt Hartroft[4] (Washington Univ )

*Steroid hormone secretion*—Restricted sodium intake alters hormone secretion by the adrenal cortex Normal men deprived of sodium increase urinary excretion of aldosterone without significant change in other adrenal hormones The authors induced severe chronic sodium deficiency in rats and killed the animals at intervals of 2 60 days The experimental animals gained weight throughout the test but at a rate significantly slower than pair fed controls Mean adrenal weights for the two groups were almost the same Therefore when adrenal weight was related to body weight the animals depleted of sodium had significant adrenal hypertrophy Concentration of serum sodium decreased and of potassium increased in the experimental animals The adrenals were incubated in vitro with ACTH and the steroids thus formed were isolated and measured The total adrenal hormone formation of control rats increased progressively as they grew In sodium deficient rats, the ability of the adrenals to form steroid hormones in vitro continued at a relatively constant and significantly lower rate throughout the experiment although the adrenal glands became hypertrophic

Normal rat adrenals release 4 steroids when stimulated in vitro by ACTH Corticosterone is secreted in greatest quan

(4) E doc logy 60 634-640 641 651 M y 1957

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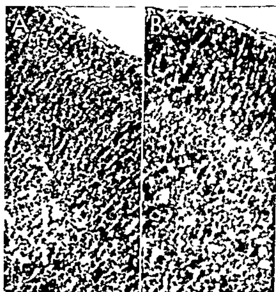
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in sodium deficiency whereas the zona fasciculata atrophies Increased aldosterone secretion accompanied hypertrophy of the zona glomerulosa and depressed glucocorticoid secretion particularly corticosterone was associated with atrophy of the zona fasciculata

When sodium depletion is sufficiently severe the zona




F g 104—F en ct n f ad enal glands of sodı m-deplet d ats. F ll width of cort x incl d d ach fig Wh m d lla n t seen t l e j t out of field at low left L p d ppea bla k n l g ay *A* 2 days f sod m defic ency zona glomerulosa b oader th n rmal but l p d d t b t n n t s g ficantly diff ent from that n nt ls note p om t lipid i e t t on between ona glomerulosa and zon f sc culata. *B* 2 week f sod m d fic y zona gl m rul sa exceed gly wide w th la g globul f l p d n t port ( l r v cu l s rep sent lipid globules d opped f m ect n d n g e tu g d t ining), t an t on one st ll evi d nt between glom los nd zona f sc cul t and l tter sh ws bes de lipid d pletio d ease n w dth O l d O h m t yl n a d l ght g n st ed ced fr m ×130 (Court y f Hart ft P M and Ei te A. B Endocrinology 60 641 651 M y 1957)

glomerulosa hypertrophies and produces more aldosterone at the expense of the zona fasciculata and its glucocorticoids The different zones and functions of the adrenal cortex can vary independently of one another Other factors besides ACTH must be involved in regulating adrenocortical growth and function

► [The mechanism of regulation of aldosterone secretion is still not clear The preceding observations indicate again that secretion of this steroid is controlled separately from the other adrenal steroids (see also 19 / 58

YEAR BOOK, p 620) Venning has recently published additional important observations pertaining to this problem (Canad. M.A J 77 773 Oct. 15 1957) —Ed.]

**Calcification of Adrenal Gland in Nontuberculous Children Two Cases** are reported by D Brunel and O Flandre[5]

CASE 1 —Boy 4 had lumbar pain for several weeks without weakness fever or weight loss Clinical examination was negative X ray of the spine showed bilateral adrenal calcifications No pigmentation was noted digestion was normal and blood pressure was 90/50 Cutaneous and intradermal tuberculin tests were negative. Retroperitoneal pneumogram confirmed presence of adrenal calcifications The only biochemical abnormality was a low blood sugar initially 71 mg /100 ml later 85 90 mg /100 ml

CASE 2 —Girl 10 with intermittent rhinobronchitis during early childhood some months after acute pyelocystitis showed vague pains in the abdomen and lumbar region which persisted in the right side of the abdomen Intravenous urography showed no abnormality of the urinary tract but revealed bilateral calcifications of the adrenal glands Asthenia pigmentation and digestive disturbances were absent Arterial pressure was 105/60 Tuberculin tests were negative. The only abnormality revealed by complete biochemical studies was hypocalcemia (7 2 mg /100 ml ) *without accompanying signs of* spasmophilia

Both patients were followed for over 1 year and no new symptoms appeared Among the etiologic factors considered and rejected in these cases the authors list tuberculosis (negative tuberculin tests and no clinical signs) hypercalcemia local hypercholesteremia adrenal cancer and local hemorrhage They suggest that calcification of an inclusion in the adrenal gland or presence of osteoid tissue (since bone and adrenal cortex have a common mesenchymal origin) might possibly have etiologic significance

► [When a question of adrenocortical hyperactivity is raised clinically two questions must be answered Does the patient in fact have excessive adrenal activity? And if so is the hyperactivity caused by hyperplasia, a benign tumor or a malignant one? In questionable cases ordinary diagnostic measures such as urine or plasma steroid levels may not be helpful The response to ACTH may be diagnostic if it is greatly exaggerated, but in some cases this response also is equivocal The following paper proposes another method for studying this problem. In certain respects this method (which derives from observations by Christy J Cl n Endocrinol 16 1059 1956) is similar to the thyroid suppression test of Werner (1956-57 YEAR BOOK p 648) —Ed ]

**Effect of Prednisone on Adrenal Responsiveness to Corticotropin in Normal Subjects and in Patients with Treated and Untreated Cushing's Syndrome** Recent studies have shown that daily administration of 30-50 mg prednisone for 7 days to normal subjects suppresses the adrenocortical re

(5) A ch f anç p d t 14 501 505 1957

sponse to ACTH as measured by plasma levels of 17 hydroxycorticoids This response is attributed to inhibition of elaboration or release of ACTH by prednisone Patients who have bilateral adrenocortical hyperfunction fail to respond this way to prednisone Jack Geller Agustin S Alvarez Aron Gutman Athos de Freitas J Lester Gabrilove and Louis J Soffer[6] (Mount Sinai Hosp New York) evaluated the results of this test in patients with Cushing s syndrome before treatment and during partial or complete clinical remission after pituitary irradiation with or without unilateral adrenalectomy

Patients with active Cushing s syndrome not due to tumor showed no suppression of response to ACTH administration after 7 days of prednisone therapy Of 4 patients in complete clinical remission as measured by clinical and laboratory criteria including normal levels of plasma and urinary 17 hydroxycorticoids 2 still responded abnormally to the prednisone test in that they showed an adrenocortical response to ACTH after 7 days of prednisone therapy In the other 2 results of the test were normal Of 3 other patients in only partial remission 2 had a persistently abnormal response to the prednisone test

The fact that patients in remission with neither clinical nor laboratory evidence of Cushing s syndrome may still show an abnormal response to ACTH after administration of prednisone suggests that this abnormality may be used as an additional aid in the diagnosis of adrenocortical hyperfunction

► [In addition to this we have seen a patient with adrenocortical hyperactivity proved at operation to be of hyperplastic origin whose elevated plasma cortisol concentration did not change after the intravenous infusion of ACTH for 5 hours I therefore feel that it is impossible to exclude tumor if the patient s steroid secretion rises after ACTH and (in disagreement with Soffer Gabrilove and Geller) that it is unsafe to make a diagnosis of tumor in patients whose plasma corticoid concentration fails to rise At present it seems best from both a diagnostic and therapeutic point of view to explore all patients with proved hyperadrenocorticism —Ed.]

**Response of Plasma 17 Hydroxycorticosteroid Level to Gel ACTH in Tumorous and Nontumorous Cushing s Syndrome** No clinical signs or symptoms can differentiate Cushing s syndrome of adrenocortical carcinoma from that due to adenoma or hyperplasia though high excretion of urinary neutral 17 ketosteroids suggests malignancy Since response to ACTH has reportedly been helpful L J Soffer J Geller

(6) J Cl Endocri 1 18 409 416 Apr 1 1958

and J L Gabrilove[7] (Mount Sinai Hosp New York) administered 40 units of Gel ACTH intramuscularly to 8 patients with classic Cushing's syndrome Plasma 17 hydroxycorticoid levels were measured before and 2 hours after the injection At surgery 3 proved to have hyperplasia 3 malignant tumor and 2 adenoma

In the 3 with hyperplasia the 17 hydroxycorticoid plasma concentration was elevated before unilateral adrenalectomy In 2 it increased further with ACTH stimulation whereas the other responded only slightly In both patients with adenoma the plasma 17 hydroxycorticosteroid level was elevated One responded to ACTH with a modest increase the other showed no change Of the 3 with malignant tumor 1 showed no change after ACTH 1 showed moderate increase and 1 showed as much increase as did the patients with hyperplasia In this patient after surgery the plasma 17 OH CS level did not increase after Gel ACTH indicating that it was the tumor which had responded to ACTH stimulation

These studies show that if plasma 17 hydroxycorticoid levels do not increase after administration of Gel ACTH an adrenocortical tumor is strongly suggested as the cause of the Cushing syndrome Presence of a normal or augmented response is not of diagnostic significance

**Adrenocortical Carcinoma with Hyperadrenocorticism Clinical Metabolic and Hormonal Study** Herta Spencer Isaac Lewin Daniel Laszlo Roy Hertz Attallah Kappas and Thomas F Gallagher[8] (New York) intensively studied a patient who had adrenal carcinoma through the early stages after removal of an adrenal tumor and then 3½ years later during the period of widespread metastases Even during the time of metastases of this highly malignant tumor hormone production was unequivocally increased by ACTH probably depressed by exogenous cortisone and significantly inhibited by Amphenone

Woman 42 *had hypertension and slight hirsutism for many years* but sudden amenorrhea and fulness of the face Blood pressure was 170/105 mm Hg and minimal hypertensive retinopathy was present X rays of the spine showed minimal osteoporosis A left adrenal *mass* was demonstrated by presacral air insufflation It was removed and histologic examination revealed an adrenocortical tumor with focal areas of bizarre cells and increased mitotic activity Thereafter

(7) J Clin E d nol 17 878-883 J ly 1957
(8) A M A A h *Int M d 100 658 668 O t b 1957*

the patient remained well except for hypoadrenalism which was treated with steroids

Facial hair recurred and she became increasingly irritable 3½ years after removal of the tumor Menses had been normal until two months before this second hospitalization On examination she had marked facial hirsutism masculine hair distribution of arms chest and abdomen moon facies and enlarged clitoris Blood pressure was elevated The liver was enlarged and nodular consistent with liver metastases Presacral air insufflation disclosed multiple masses in the adrenal area At operation she had widespread metastases which on biopsy were found to be carcinoma of adrenal origin Cortisone was continued postoperatively then tapered but the temperature rose to 103 F and blood pressure dropped to 95/70 When the dose of cortisone was increased improvement was prompt Six weeks after surgery cortisone was gradually withdrawn

Amphenone was administered 0 5 0 75 Gm every 3 hours Drowsiness temperature rise and decrease in blood pressure forced reduction in the dose The areas of hepatic metastases became tender and appeared to decrease in size She died subsequently

*Before the first operation the urine contained* normal amounts of androsterone and dehydroisoandrosterone but increased amounts of the 11 oxygenated steroids and etiocholanolone After removal of the tumor excessive amounts of these steroids disappeared With recurrence of symptoms of hyperadrenalism secondary to functional metastases 11 oxygenated steroids returned to excessive levels and androsterone and etiocholanolone increased markedly The most striking increase was in dehydroisoandrosterone

With corticotropin stimulation the dehydroisoandrosterone increased markedly and to a lesser degree the other steroids also increased This was unequivocal evidence that the neoplasm responded to adrenocorticotropin Exogenous cortisone induced a significant depression of tumor steroidogenesis particularly in the amounts of 11 desoxysteroids During Amphenone therapy steroid production by the tumor was reduced strikingly

These results establish clearly that unresponsiveness to exogenous or endogenous hormonal control cannot be considered a distinguishing characteristic of adrenocortical malignancy The functional status of these tumors must be individually considered in detail

**Mechanism of Adrenal Atrophy in Cushing s Syndrome Due to Adrenal Tumor** Atrophy of the contralateral adrenal gland is characteristic of Cushing s syndrome due to an adrenal tumor It results from pituitary suppression by the

excessive corticoid hormones secreted by the tumor inhibiting production or release of ACTH The same type of adrenal atrophy is associated with cortical hormone therapy It has previously been considered that ACTH given to patients so affected will permanently reactivate the adrenal glands which have been suppressed and may even prevent adrenal atrophy if given during cortisone therapy Laurence H Kyle Richard J Meyer and John J Canary[9] (Georgetown Univ ) in studying 2 patients who had compensatory adrenal atrophy due to an adrenal tumor obtained evidence which makes such an opinion doubtful

Woman 23 before a benign adenoma was removed from the left adrenal gland excreted an average of 9 mg 17 ketosteroids daily After surgery she excreted 4 mg daily and part of this was attributable to cortisone therapy Intravenous ACTH increased the excretion moderately After all treatment was stopped excretion was less than 2 mg /day At this time all appetite was lost and profound weakness appeared Arthralgia and headache became severe and the patient was again hospitalized 4 weeks after surgery Epinephrine induced eosinopenia but had no effect on 17 ketosteroid excretion. Two successive daily infusions of ACTH induced more marked eosinopenia a moderate rise in 17 ketosteroids and significant symptomatic improvement but symptoms soon recurred and persisted

During pregnancy 13 months after surgery symptoms were ameliorated and 17 ketosteroid excretion rose to normal but after delivery symptoms recurred and 17 ketosteroid excretion was less than 5 mg daily Two years after surgery ACTH was again infused on 2 successive days for 8 hour periods followed by 40 units of ACTH gel every 6 hours for 8 doses Response was dramatic 17 ketosteroids rose sharply weight increased the face became round and plethoric and the abdominal striae intensely red with cessation of therapy these symptoms of hyperadrenalism subsided Thereafter the patient was symptomatically well and 6 years after surgery her health is excellent with no evidence of adrenal dysfunction

Many reports stress adrenal atrophy in similar cases but little attention has been paid to its duration Most important was the observation that though the atrophic adrenal gland may be stimulated this reactivation was not well maintained It appears that suppression of endogenous ACTH production and secretion may be profound and protracted Though the atrophic adrenal gland may be restored to normal or supernormal activity by exogenous ACTH this effect is not maintained after stimulation is stopped The relative ease with which the atrophic gland may be activated

(9) N w E gla d J M d. 257 57 61 J ly 11 1957

should not be construed as an indication that the activation will last

Until more definitive data are obtained suggested treatment is as follows In the early postoperative period substantial amounts of cortisone should be given which should be tapered more slowly and for 5 6 weeks the dose should be above that ordinarily required for maintenance During this period several days of intense ACTH stimulation should be used to test the adrenal s responsiveness and to counteract excessively prolonged adrenal atrophy Cortisone should then be tapered off to 5 10 mg daily continued for several months Exogenous ACTH should be given periodically During times of stress large amounts of cortisone must be added

► [This important case documents clearly the fact that after subtotal adrenalectomy for hyperadrenocorticism ACTH secretion may be deficient. Experience with patients such as this has been a factor in persuading me that bilateral total adrenalectomy is preferable to subtotal adrenalectomy since rehabilitation is more rapid and the possible risk of subsequent recurrence is eliminated This problem has been discussed in previous YEAR BOOKS (1956 57 p 638 1957 58 p 629)

In previous years I have discussed the desirability of obtaining an adrenocorticolytic drug comparable in activity to the thiourea derivatives in respect to the thyroid The possible use of Amphenone and its limitations has also been mentioned. Recently a new material (dichloro-diphenyl dichloro ethane usually contracted to DDD) has engaged the interest of a group of investigators Although the material has not yet been tested in man preliminary reports on animal experiments may be found in Endocrinology 62 326 332 1958—Ed ]

**Urinary Estrogen Excretion in Cushing s Syndrome** Since 1933 it has been known that this excretion is high No obvious physical signs are apparent and it is unlikely that estrogens play a major role in the pathologic physiology of the syndrome However atrophy of the gonads and accessory sex organs with suppressed sexual function in men retention of sodium chloride and water and disturbed fat metabolism might be causally related Charles D West Barbara Damast and O H Pearson[1] (New York) studied a postmenopausal woman aged 58 with adrenocortical carcinoma and Cushing s syndrome

By countercurrent distribution and paper chromatography estrone and estriol were identified and isolated in a fluorometrically homogeneous form During the control period the patient excreted 5 7 µg estrone and 34 2 µg estriol/day With administration of ACTH excretion of es

(1) J Cli Endoc i ol 18 15 7 J ua y 1958.

trone increased 12 fold and of estriol fivefold The isolated estrogens were assayed for biologic activity and the positive results were in reasonable agreement quantitatively with the fluorometric measurements The acetate derivatives of the isolated estrogens behaved by paper chromatography in a manner identical with that of appropriate reference standards of authentic estrogen acetates No estradiol $17\beta$ was found in the control urine but traces were detected during ACTH administration

The relatively high urinary excretion of estrone and estriol by this postmenopausal woman and the increased estrogen excretion with ACTH stimulation suggest that these estrogens or their precursors were produced by the adrenocortical carcinoma and that this function of the tumor tissue is not autonomous but can be influenced by ACTH Excretion of estrogens in patients with adrenocortical carcinoma is highly variable Some excrete no identifiable estrogens even after administration of ACTH

Stimulation of steroid production by exogenous ACTH and suppression by corticoids suggest that endogenous ACTH may exert some control over growth and function of cancerous adrenocortical tissue If this is true patients of this type might benefit from hypophysectomy

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## THE THYROID GLAND

**Determination of Basal Rate of Oxygen Consumption by Open and Closed Circuit Methods** The closed circuit method for measuring oxygen consumption is in almost universal clinical usage Ward S Fowler Charles M Blackburn and H Frederic Helmholz Jr[2] (Mayo Clinic and Found ) compared this method with the more accurate open circuit method and with the newer laboratory methods for evaluating thyroid function the protein bound iodine concentration and radioiodine utilization

During closed circuit tests nasal expiratory leaks occurred in 3 patients and could not be eliminated The apparent BMR in these tracings would have been 20 50% too high When the results obtained by the closed circuit method were

(2) J Cl E doc L 17 786-796 J 1957

compared with those of the open circuit method in 48 patients a correlation was present but not close It was felt that in 12 of 21 clinical management would have been altered in some way had the closed circuit value been accepted instead of the more accurate open circuit value In 10 of the 12 this occurred when the two values were on opposite sides of a 15% deviation from the average normal

Similar discrepancies between the results of consecutive measurements by open and closed circuit methods have been reported by others with differences varying from 5 to 12% A standard error of the closed circuit method of about 2 3 Calorie/sq m /hour or about 6 7% is clinically important since this is almost equal to the interindividual variability of the healthy population which has a standard deviation of about 2 5 Calorie/sq m /hour Such a method is limited by its inability to detect small deviations from normal and to measure accurately changes of moderate magnitude The error of the open circuit is less than 1% of the usual metabolic rate

Leakage of gases may occur around the mask mouthpiece or noseclip With the closed circuit method net inspiratory leaks add gas to the system and cause falsely low values for oxygen consumption Tests are not usually made for such leaks In contrast outward leaks of expired air in the open circuit method cause falsely low results but only about 1/25 the error that would be produced by comparable losses in the closed circuit method In the closed circuit method an expiratory leak of only 1 ml /breath about 15 ml /minute produces a false elevation of 5% or more in the BMR

The usual method of noting a change in slope of the recording to detect large leaks is of little use because it is doubtful that a 5 10% change in slope can be detected within the usually recommended period of 1 2 minutes especially if the breathing is irregular and if detection must be made by visual inspection during the procedure

The basal metabolic rate is satisfactorily measured by the open circuit method The closed circuit method is less accurate and liable to much greater errors

**Individual Variations in Expenditure of Energy** In any homogeneous group of adults or children some have calorie intake greatly in excess of others which is unexplained by size or obvious muscular activity Persons who outwardly

appear similar expend surprisingly different amounts of energy in lying sitting and standing J Booyens and R A McCance[3] (Univ of Cambridge) measured the metabolism of 36 normal adult volunteers (22 men) during late morning or afternoon about 4 hours after the previous meal A comfortable bed and an upright chair were available

The metabolic rate of some subjects differed widely from the group average while lying sitting and standing Some had exceptionally low expenditures and some exceptionally high expenditures of calories These unusual rates were maintained for months and must be accepted as permanent or semipermanent characteristics Since adults and children spend so much of their 24 hours lying sitting and standing a person with consistently low rates at all 3 positions requires less food than does a person of similar build with a consistently high rate This may be the only important difference in persons who lead outwardly similar lives and must be considered together with the obvious and visible differences in active physical work These masked variations in expenditure of energy explain why some persons require few calories to maintain weight and others twice as many but there is nothing to suggest that they are important in the fundamental control of appetite

The intensive search for new syndromes and for new opportunities to apply new remedies has led to the description of a condition characterized by a low basal metabolic rate with one or more of the following symptoms but no other signs of myxedema or subnormal function of the thyroid gland lethargy easy fatigability nervousness irritability emotional instability sensitivity to cold headache ill defined skeletal pain diminished sexual potency in the male and menstrual irregularity in the female It is claimed that these persons will respond to triiodothyronine but not to thyroid extract or to thyroxin If this becomes public knowledge there is a risk that many patients who come to general practitioners with a vague story covered by these equally vague symptoms will be given triiodothyronine Such use of triiodothyronine is unjustifiable and should be discouraged Normal healthy persons may have an exceedingly low BMR It has still to be proved that a BMR 30 35% below

(3) La et 1 225 229 F b 1957

the average is necessarily abnormal The experience of many investigators suggests that it is not

► [The development of specific methods for studying thyroid function, such as radioactive iodine and blood hormone analyses has tended to push the basal metabolic rate into disrepute Unfortunately many hospitals and physicians already are equipped to determine the basal metabolic rate and are therefore reluctant to abandon it The previous article has convinced me at any rate that the ordinary closed circuit method is inaccurate and potentially misleading The expense and difficulty involved in performing an accurate open-circuit test are not appreciably less than for the newer and far more specific diagnostic methods Although rare instances may arise to justify determining the BMR in my own practice I have come to rely exclusively on radioactive iodine and serum hormonal iodine especially the highly specific butanol extractable iodine (BEI) determinations for diagnostic purposes Some of my reasons for this attitude are outlined in the following article —Ed ]

**Clinical Significance of Serum Butanol Extractable Iodine** The level of serum butanol extractable iodine (BEI) or thyroxin like iodine is a specific diagnostic criterion for evaluating thyroid function and therapy The protein bound or serum precipitable iodine (PBI SPI) is a convenient assay of thyroid function in most patients but in some it disagrees with the clinical status The active circulating hormone of the thyroid gland is believed to be thyroxin like and thyroxin is extractable in butanol The BEI levels correlate better with the clinical status of thyroid function and can be measured accurately even after administration of inorganic or radioactive iodine Evelyn B Man and Philip K Bondy[4] (Yale Univ ) review their experiences with the BEI determination

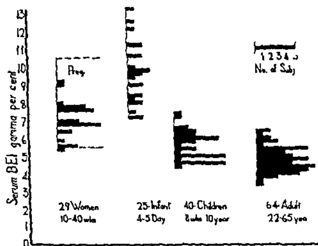
Normal BEI levels are given in Figure 105 The BEI measures organix iodine compounds precipitated with protein and when thyroxin triiodothyronine triiodothyroacetic acid and tetraiodothyroacetic acid are added in vitro they are quantitatively recovered in the BEI assay Triiodothyronine in vivo does not increase the serum BEI Diiodotyrosine as much as 32 μg /100 ml and inorganic iodine as much as 1 000 μg /100 ml in vitro have no effect but organic iodine compounds given for diagnostic or therapeutic purposes cause contamination

When a patient has received inorganic iodine the concentration of SPI may be falsely elevated by 2 10 μg /100 ml compared to the level of BEI In such cases the BEI agrees more closely with the clinical status than does the SPI which may not truly reflect the clinical state Such elevations

(4) J Clin Endocrinol. 17 1373 1383 N mber 195:

may be caused by iodide ingested in any of the many preparations which include iodide often unknown to the patient There are over 300 pharmaceutical products which might cause iodide contamination many of them in superficially unimpressive forms such as vitamins or tonics

In patients with Hashimoto s syndrome the BEI is in better agreement with the clinical impressions of hypo or




F g 105 —Histog m f rum BEI le l n g oup f uthy d perso ranging f om i f t t adult At l ft b oken l es den t g d n d f om e lt of 114 BEI det rm t on in 33 thy d p g nt w men between the 10th nd 40th weks f p gna y each u t in bla k ba (se k y hart) p ese t rag l for ach of 29 women I th ge g oups ea h u t bla k ba p se ts BEI lev l s gl bject (Court y f Ma E B d Bondy P K J Clin Endoc l 17 1373 1382 N ember 1957 )

euthyroidism than are the results of radioactive iodine tracer tests or the PBI values (which are sometimes elevated to the hyperthyroid range) When replacement therapy is given the excess of PBI over BEI decreases simultaneously with reduction in size of the goiter

Determination of the serum BEI as a test of thyroid function has two advantages (1) it is unaltered by administration of iodides and (2) it measures the thyroxin like compounds of the serum Discrepancies between PBI and BEI values may sometimes be useful in diagnosing thyroiditis or nontoxic goiter in which the gland is unable to secrete normal thyroid hormone In patients treated with radioiodine

the average is necessarily abnormal The experience of many investigators suggests that it is not

► [The development of specific methods for studying thyroid function, such as radioactive iodine and blood hormone analyses has tended to push the basal metabolic rate into disrepute. Unfortunately many hospitals and physicians already are equipped to determine the basal metabolic rate and are therefore reluctant to abandon it The previous article has convinced me at any rate that the ordinary closed circuit method is inaccurate and potentially misleading The expense and difficulty involved in performing an accurate open circuit test are not appreciably less than for the newer and far more specific diagnostic methods Although rare instances may arise to justify determining the BMR in my own practice I have come to rely exclusively on radioactive iodine and serum hormonal iodine especially the highly specific butanol extractable iodine (BEI) determinations for diagnostic purposes Some of my reasons for this attitude are outlined in the following article —Ed ]

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(4) J Cl Endocri L 17 1373 1383 Novembe 1957

uptake during testosterone therapy In this group there were no clinical changes of significance

A fall in the circulating PBI level during testosterone medication might occur as a result of (1) a change in the thyroxin binding capacity of plasma (2) a change in renal iodine clearance (3) increased utilization of thyroxin or (4) decreased thyroid output of thyroxin In the absence of clinical and laboratory signs of hypothyroidism the low PBI concentration can best be explained by the first of these mechanisms

**Thyroidal Uptake and Plasma Clearance of $I^{131}$ and $I^{127}$ in Cirrhosis of Liver** have previously been reported to be increased above 50% in almost half the patients tested Reginald A Shipley and Ethel Buchwald Chudzik[6] (Western Reserve Univ ) studied 36 patients with proved hepatic cirrhosis and found high values for thyroidal uptake clearance or conversion ratio of $I^{131}$ in 8. In 5 the 24-hour thyroidal uptake exceeded the upper limit of 45% reached by the control group 7 had clearances exceeding 40 ml /minute and the conversion ratios in 5 were well above the normal range $PBI^{131}$ activity in the serum was high in 4 patients A butanol alkali extraction procedure confirmed the high ratio of hormonal to total $I^{131}$ activity shown by a high $PBI^{131}$ conversion ratio When the complete series of $I^{131}$ tests was repeated in 3 patients after 1 2 months of hospitalization all values were normal

Of the 8 patients with abnormal $I^{131}$ values 3 had a high uptake of $I^{127}$ in these serum inorganic concentration and urinary excretion of $I^{127}$ were also greater than average In the other 5 $I^{127}$ uptake was below average serum levels were low and excretion was less than normal In all 8 patients serum $PBI^{127}$ levels were below 7 5 µg /100 ml

About one third of the patients with cirrhosis were receiving a full diet seasoned with iodized salt but in two thirds salt intake was restricted Excretion of iodine tended to vary with degree of salt restriction abnormal $I^{131}$ values were more frequent among the group whose intake of salt was restricted

The amount of $I^{131}$ taken up by the thyroid gland per unit of time is proportional to functional activity of the gland and to plasma concentration of $I^{131}$ Iodide uptake in itself is

(6) J Cl E doc 1 17 1229 1236 Oct be 1957

the thyroid may secrete iodinated compounds not found normally in the blood stream Clinical progress cannot be evaluated by thyroidal uptake of radioiodine or the serum PBI Determination of the BEI which is unaffected by the metabolic abnormality of the thyroid gland can accurately assess thyroid function during treatment

**Marked Depression of Plasma Protein Bound Iodine Concentration in Absence of Clinical Hypothyroidism during Testosterone Medication** is reported by Hans G Keitel and Max G Sherer[5] (Nat l Inst of Health) For this study 6 dwarfed prepubertal children received 25 mg methyltestosterone orally 3 or 4 times daily for about 40 days, and 7 women with mammary cancer received 50 mg testosterone propionate intramuscularly 3 times a week for 15 55 days

The control plasma protein bound iodine concentrations in the 6 children were within normal range During oral methyltestosterone medication the PBI level dropped in 5—in 4 to within the hypothyroid range The fall occurred as early as the 12th day and was sustained during the next 3 weeks After methyltestosterone was discontinued the PBI level returned to the normal range by the 30th day

The 24 hour thyroid $I^{131}$ uptake was determined with and without testosterone in 5 of the 6 children In 4 a lower uptake was observed during administration of testosterone but in only 1 did the uptake fall definitely below normal In the 5th patient there was no change

In the group as a whole weight gains of 10 15% and an increase in appetite and activity were noted No untoward reactions occurred except a moderately pronounced acneiform rash and deepening of the voice in 1 patient The pre breakfast blood pressure readings and pulse rates did not change during testosterone medication Although the skin tended to become pinker there was no change in texture No tendency toward constipation was noted

The findings in the 7 women were similar to those in the 6 children In all there was a drop in the level of plasma PBI during testosterone therapy The thyroid $I^{131}$ uptake in 4 women fell slightly during testosterone medication but in 2 there was no change In the only patient who was studied for more than 3 weeks and who did not have a pronounced fall in PBI concentration there was a rise in thyroid $I^{131}$

(5) J Clin Endoc nol 17 854 861 J ly 1957

efficiently thereby making that iodide available for reuse by the thyroid Such a mechanism could increase the utiliza tion efficiency of dietary iodide Low iodine diets might potentiate goiter production by thyroxin depletion and an increased iodine intake could possibly alleviate the goiter

Finally these mechanisms make it important to consider liver and gastrointestinal function as well as the absolute amount of iodine available as possible causes of goiter

► [A somewhat comparable situation is described in mice on a high sodium diet by Isler LeBlond and Axelrod (Endocrinology 62 159 1958) —Ed ]

**Peptide Linked Iodotyrosines and Iodothyronines in Blood of Patient with Congenital Goiter** The metabolic defects in the thyroid gland associated with goiter and hy pothyroidism include inability to organify trapped iodide a defect in deiodination of iodotyrosines and possibly im paired conjugation of iodotyrosines Leslie J DeGroot Sholem Postel Jorge Litvak and John B Stanbury[8] (Har vard Univ ) report a patient who had a different metabolic abnormality

Woman apparently normal at birth did not walk until aged 2 or talk until aged 3 and had goiter observed at age 8 She was short obese and dull with the facies of mild cretinism and a firm nodular thyroid gland 5 times normal size Serum cholesterol level was 329 mg /100 ml Subtotal resection of the goiter was performed at age 15 and pathologic diagnosis was multiple fetal adenomas She was main tained on desiccated thyroid and became alert menses continued nor mally On her return to the thyroid clinic at age 28 there were no symptoms except constipation attributable to hypothyroidism The tongue was larger than normal and the skin dry Hands and feet were puffy axillary and pubic hair sparse and breasts massive The thyroid was twice normal size The BMR was −14 and −36% serum cholesterol levels 326 and 348 mg /100 ml PBI 2 µg /100 ml and the 24 hour uptake of $I^{131}$ by the thyroid 57%

Intravenously administered $I^{131}$ labeled diiodotyrosine and thy roxin were metabolized normally Electrophoresis of plasma proteins after in vitro addition of $I^{131}$ labeled thyroxin demonstrated normal amounts of thyroxin binding protein There was rapid concentration of $I^{131}$ by the thyroid gland and administration of potassium thio cyanate did not cause the release of trapped iodide Endogenously labeled material in the serum was 60-65% insoluble in butanol The soluble fraction proved to be thyroxin and triiodothyronine. Starch block electrophoresis and ultracentrifugation identified the butanol insoluble portion as an abnormal iodinated protein having the mo bility of albumin This protein was not precipitated by equine antihuman serum albumin After enzymatic hydrolysis of plasma mono and diiodotyrosine thyroxin and triiodothyronine were iden tified on paper chromatograms

(8) J Cl E doc 1 18 158-166 F b ry 1958.

not a measure of total thyroid function None of these patients exhibited clinical evidence of hyperthyroidism and the normal serum PBI values supported the concept of normal thyroid function

Accelerated thyroidal uptake dissociated from augmented hormone secretion is a classic finding in patients who have a dietary deficiency of iodine A pre existing dietary deficiency best explains the occurrence of enhanced thyroidal avidity for iodide in certain cases of alcoholic cirrhosis

► [In using any test it is important to keep in mind the factors which may cause misleading results Some of the potential sources of error in blood iodine and $I^{131}$ tracer studies are mentioned above —Ed ]

► ↓ The next 3 papers advance further our understanding of the mechanisms which produce nontoxic goiters (Previously published material has been summarized in the 1957 58 YEAR BOOK p 643 ) It is now apparent that goiters may occur as a result of insufficient supplies of iodine or as a result of "wasting of iodine when this element is incorporated into physiologically inactive substances The next paper introduces a new idea however—that is that thyroxin itself may be "wasted" under certain circumstances —Ed

**Thyroxin Excretion Possible Cause of Goiter** is discussed by L Van Middlesworth[7] (Univ of Tennessee) Soy bean flour has been observed to cause in rats a high uptake goiter which is not readily inhibited by iodide therapy The author investigated the possibility of soy flour causing an increased fecal thyroxin excretion

Rats given an intraperitoneal injection of 1 2 μg $I^{131}$ thyroxin excreted the thyroxin at rates dependent on their diets Soy flour and laboratory chow caused excretion rates 2 20 times greater than control diets

Thus loss of thyroxin via the feces may so increase the daily requirement of thyroxin that the thyroid gland may be overtaxed to produce the hormone The mechanisms by which soy flour cellulose bran or standard laboratory chow increase this loss have not been clarified There are several possibilities (1) mechanical i e the fecal mass may be so great that fecal contents may move too fast to afford reabsorption of biliary thyroxin (2) the rate of bile production or thyroxin concentration in the bile may be altered by certain dietary substances (3) the capacity of the intestine to reabsorb thyroxin secreted into the intestine may likewise be chemically altered by some substances and (4) thyroxin remaining in the intestine for prolonged periods may be destroyed by bacteria so that thyroxin iodide is released more

(7) Endocrinology 61 5 0-573 Nov mbe 1957

was not true in the present patient The data suggest that desiccated thyroid may have been somewhat more effective than either of the two thyronines

It is likely that the delayed responses to thyroid hormone of this patient as contrasted with those in the usual patient with nontoxic diffuse goiter are simply the result of the un usual degree of *pituitary secretory activity It is also pos* sible that pituitary suppression is not the only factor in volved and that there may be a suppressive effect directly on the thyroid gland Thus the greater efficacy of desiccated thyroid might be explained by an inhibitory effect on the thyroid gland of iodide made available from the inorganic iodine monoiodotyrosine and diiodotyrosine in the desic cated thyroid preparation—similar to the effect of iodides in toxic goiter

► [Other interesting and important papers relating to this problem include studies by Cassano Baschieri and Adreani (Helvet. med. acta 3 216 1957) who found iodide wasting via the urine in certain goitrous women by Pitt Rivers Hubble and Hoather (J Clin. Endocrinol 17 1313 1957) Di George and Paschkis (J Clin Endocrinol 17 645 1957) and Stanbury and McGirr (Am J Med. 22 712 1957) Bansi has reviewed the problem (Schweiz med. Wchnschr 88 25 Jan. 11 1958) —Ed ]

**Plunging Goiter Made Evident by Valsalva s Maneuver** Cervical goiter extends to just beneath the sternum in 7 21% of all goiters operated on Goiters which patients have noted to disappear apparently spontaneously have been subse quently identified in the thorax The totally intrathoracic goiter which cannot be felt in the neck is much rarer than the partially intrathoracic goiter A mobile gland that can disappear from the neck or can pop into view is even more rare This is termed the plunging or bobbing goiter Everett Shocket and Theodore R Hudson[1] (VA Res Hosp Chi cago) observed a patient whose intrathoracic goiter was not palpable with the classic maneuver of swallowing with the head slightly flexed forward but which was readily detected when he simply strained as in the performance of the Val salva maneuver (Figs 106 and 107)

Typically when a plunging goiter slips into the thorax it presses on the trachea sufficiently to embarrass respiration and produce characteristic frightening choking spells The patient soon learns that by coughing or otherwise strain ing the gland can be popped back into the neck and the re

(1) A M A. A h. S g 75 135 137 J ly 1957

This patient apparently had a congenital thyroid abnormality characterized by release of large quantities of a metabolically inactive iodinated protein into the serum The protein may have been related to thyroglobulin Trypsin did not completely hydrolyze this protein in contrast to normal thyroglobulin which supports the hypothesis that an abnormal thyroprotein had been formed

Except for the presence of large amounts of diiodotyrosine the abnormal substance described shared the properties of compound X observed in the serum of some patients with thyroid carcinoma It may be the factor in other cases of goiter in which iodinated compounds in the blood are incompletely extractable in butanol and is possibly related to the non butanol extractable fraction of the protein bound iodine reported in patients with chronic lymphocytic thyroiditis

**Pathogenesis of Case of Congenital Goiter with Abnormally High Levels of SPI and with Mono and Diiodotyrosine in Serum** Sidney C Werner Richard J Block Richard H Mandl and A A H Kassenaar[9] (New York) present a case of congenital goiter in a girl aged 5 with mild hypothyroidism The serum precipitable iodine (SPI) level was about 25 μg/100 ml On paper chromatography the SPI was equally distributed among monoiodotyrosine diiodotyrosine triiodothyronine and thyroxin Studies of thyroidal and peripheral dehalogenation of labeled diiodotyrosine revealed the presence of dehalogenase activity in nearly normal amounts

In general the stimulus to augmented activity of the thyroid as well as to hyperplasia and hypertrophy is considered to be an increased rate of release of thyrotropin by the anterior pituitary consequent to a lowered level of circulating thyroid hormone This sequence was suggested in the authors patient by the fact that thyroidal $I^{131}$ uptake SPI levels and gland size decreased on administration of thyroid hormone However the extent and rate of suppression of these three indexes were limited and slow In most patients with nontoxic diffuse goiter and in healthy persons uptake and release are successfully inhibited within a week when triiodothyronine thyroxin or desiccated thyroid is given These values become virtually zero after several weeks This

(9) J Clin Endocrinol 17 817 831 July 1957

was not true in the present patient The data suggest that desiccated thyroid may have been somewhat more effective than either of the two thyronines

It is likely that the delayed responses to thyroid hormone *of this patient* as contrasted with those in the usual patient with nontoxic diffuse goiter are simply the result of the unusual degree of pituitary secretory activity It is also possible that pituitary suppression is not the only factor involved and that there may be a suppressive effect directly on the thyroid gland Thus the greater efficacy of desiccated thyroid might be explained by an inhibitory effect on the thyroid gland of iodide made available from the inorganic iodine monoiodotyrosine and diiodotyrosine in the desiccated thyroid preparation—similar to the effect of iodides in toxic goiter

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(1) A M A A h S g 75 135 137 J ly 1957

removal of the goiter, these abnormal levels slowly returned to the normal range

The known association of gamma globulins with circulating antibodies and the infiltration of the diseased thyroid with plasma cells and lymphoid tissue (which are known to produce antibodies) suggested that the disease process and postoperative findings might be explained if it were postulated that these patients were immunized against an antigen in the thyroid gland

The serum of patients with Hashimoto s disease revealed autoantibodies against human thyroglobulin by diffusion precipitation reactions in agar gels The antibody was organ specific and did not cross react with extracts of the thyroid gland from any of six other mammalian species

Of 144 patients with Hashimoto s disease who were operated on the precipitin test was positive in 109 The antibody level was highest in untreated patients weaker or negative precipitin reactions were obtained in 25 patients with Hashimoto s disease after thyroidectomy Thyroglobulin precipitins were also found in the serums of 6 patients with spontaneous nongoitrous myxedema of 5 with subacute (giant cell) thyroiditis and in 1 with active untreated thyrotoxicosis No precipitins were found in the serums of 238 patients with various thyroid disorders

It is suggested that destruction of the thyroid in Hashimoto s disease results from progressive interaction of the autoantibody with thyroglobulin in the gland and that the lesser degrees of lymphoid infiltration found in other thyroid diseases may represent a localized immune response

► ↓ Acute and subacute thyroiditis may present a puzzling picture to the clinician Some of the practical problems involved are discussed in the next 2 papers —Ed

**Subacute Thyroiditis Disease Commonly Mistaken for Pharyngitis** Robert Volpe and MacAllister W Johnston[3] (Univ of Toronto) review 56 cases The disease process actually may be acute subacute or chronic self limiting inflammation of the thyroid gland The cause is unknown Subacute thyroiditis is characterized by fever malaise and firm tender enlargement of the thyroid gland with variable often prolonged course It is separate and distinct from Hashimoto s or Riedel s struma and is more common than both these conditions together There was preponderance of fe

(3) Ca d M A J 77 297 306 A g 15 1957



Fg 106 (l ft) —P t ent at e t
Fg 107 ( ight) —Pat ent d i g Vals l m n u r N te m th t s mt neck.
(Court y f Shock t E and Hud n T R. A M A A h. Su g 75 135 137 July 1957 )

spiratory and choking discomfort can be relieved X rays of the area in conjunction with Valsalva s maneuver are helpful in diagnosis

► [Subacute thyroiditis has recently engaged the interest of investigators from many fields Eylan Zmucky and Sheba for example have isolated a virus they believe to be identical with mumps virus from thyroid tissue obtained from 2 patients who developed subacute nonsuppurative thyroiditis (Lancet 1 1062 1957) during an epidemic of ordinary mumps The possibility that autoimmune mechanisms may play a part in the disease or in the development of lymphocytic thyroiditis has also been raised —Ed ]

**Autoimmunity in Hashimoto s Disease and Its Implications** are discussed by Deborah Doniach and I M Roitt[2] (Middlesex Hosp London) High values for gamma globulins and for the results of flocculation tests have been observed in the serum proteins of patients with Hashimoto s disease The highest values have been obtained in untreated patients with large goiters During the months following

(2) J Clin Endocrin 1. 17 1293 1304 November 1957

toxic adenoma hemorrhage into a cyst nodular goiter adenoma of the thyroid colloid goiter Riedel s struma carcinoma of the thyroid and myxedema Silverman needle biopsies may be helpful but seldom are indicated Diagnosis almost always can be made from clinical signs and symptoms The finding of reduced radioactive iodine uptake is helpful

The pathologic process began with acute inflammatory destruction of the follicles with edema and polymorphonuclear leukocyte infiltration Many histiocytes then appeared the colloid stimulated giant cell formation and the whole lesion appeared granulomatous Fibroblastic proliferation appeared later With recovery the granulomatous reaction and follicles regenerated but variable amount of permanent interstitial fibrosis remained

The disease usually responds to radiation therapy in total dosage of 200 400 r Cortisone and ACTH are valuable and may be the treatment of choice Both of these measures shortened or suppressed the acute phase of the disease

**Thyroid Function and Metabolism of Iodine in Patients with Subacute Thyroiditis** This disease is puzzling in etiology and pathologic physiology Tests of thyroid function are paradoxic thyroid uptake of radioiodine is characteristically diminished whereas concentration of circulating hormone iodine and BMR may be increased decreased or normal Impaired formation of new hormone and passage of pre formed stores of hormone through disrupted follicular walls into the circulation would explain these results Sidney H Ingbar and Norbert Freinkel[4] verified this hypothesis in studies in 10 patients

Each patient had the usual history and physical findings of subacute thyroiditis viz pain and tenderness over the thyroid gland often radiating to the jaw or occiput pain on swallowing marked asthenia and in some chilly sensations and fever Several had symptoms of hypermetabolism including nervousness increased sweating and weight loss

The 4 and 24 hour thyroidal uptake of radioiodine was markedly decreased during the active inflammatory phase As 9 patients denied taking any iodine the iodide stores could not have been *abnormally large Thus the diminished*

(4) A M A A b I t M d 101 339 346 F bru ry 1958

males to males 52 4, in this series, and the disease was commonest in the 4th and 5th decades In acute thyroiditis onset was sudden with severe pain in the region of the thyroid gland fever of 103 104 F and marked systemic reaction In the mild chronic disease the thyroid gland was enlarged but there was little or no tenderness, slight or no pain little or no fever and few systemic symptoms

Almost all patients had pain in the region of the thyroid or in the anterior aspect of the neck in some the pain radiated to the ears Some complained of sore throat but on being asked to localize the pain more precisely referred it to the thyroid gland and some had pain on swallowing Some patients had a prodromal period of malaise and fatigue that lasted several days During the acute phase 26 patients complained of symptoms suggesting hyperthyroidism with increased nervousness sweating heat intolerance and tachycardia Two in a late phase of thyroiditis complained of sluggishness dry hair and skin cold intolerance and low husky voice

The most characteristic sign was enlargement of the thyroid gland usually with tenderness Degree of enlargement was never great seldom did the gland become twice normal size but it always became firm to hard in consistency The spontaneous course of the disease varied average duration was 2-4 months but severe cases lasted longer Of the 26 patients with a clinical state simulating hyperthyroidism 11 subsequently passed through temporary hypothyroidism In none of the 56 patients did permanent myxedema develop nor Riedel s struma Hashimoto s struma hyperthyroidism nor carcinoma.

In early stages as inflammation destroyed the gland thyroid hormone was liberated resulting in high serum protein bound iodine increased metabolic rate and signs and symptoms of hyperthyroidism In less severe inflammation the PBI was not always elevated and the patient remained euthyroid The 24-hour radioactive iodine uptake usually was depressed often to zero because the damaged cells could not trap the iodine Erythrocyte sedimentation rate was elevated often markedly

Initial diagnoses often were erroneous The commonest error was calling the condition pharyngitis Other erroneous diagnoses included tonsillitis earache, hyperthyroidism

10 26 years Of the 17 patients 15 were females Age at time of original treatment was 8 56 years with 10 being under 37 and the others 53 56 Duration of persistence was 10 14 years in 9 and 17 years or over in 8

The type of the original tumor and that of the final tumor were histologically identical in 16 The commonest type of original tumor was follicular (8 cases) followed by 4 papil lary carcinomas 2 mixed papillary and follicular carcino mas and 3 undifferentiated carcinomas of which 1 was the giant cell variety Initial treatment included excision of the tumor x irradiation and radical neck dissection Six patients had local excision only 8 had local excision followed by ir radiation and 3 had radical neck dissection plus irradiation Six received desiccated thyroid after surgical therapy

Persistent tumor was limited to the neck in 9 6 had no re currence in the neck In 2 there was tumor in the neck and distant sites Of the metastatic site beyond the neck the lung was the most frequent There were 6 cases of metastasis to the lung 4 to bone 1 to the brain and 2 to more than 1 viscus Of the 7 deaths 5 were attributed to thyroid cancer—2 from local extension 2 from disseminated metastases and 1 from metastasis to the brain

Prolonged persistence of thyroid cancer cannot be pre dicted on the basis of histology Every major type of thyroid cancer was observed including undifferentiated carcinoma of the giant cell type usually considered the most malignant of all thyroid tumors Long persistence of thyroid cancer is not limited to persons in the younger age groups

As a group these patients did not have what would be considered either vigorous or even adequate initial surgery

**Thyropituitary Relationships in Children with Cretinism and Hypothyroidism** A fine balance between the pituitary and the thyroid has long been assumed and is supported by considerable indirect evidence but direct measurements have failed to confirm a reciprocal regulatory control in a strict sense Angelo M Di George Savino A D Angelo and Karl E Paschkis[6] (Philadelphia) present additional data on 5 hypothyroid (cretinous) and 3 euthyroid infants and children

The levels of thyrotropic hormone (TSH) in the 3 euthy roid subjects were in the same range previously found in

(6) J Cl E doc 1 1 842 848 J ly 1957

percentile accumulation of iodine by the thyroid glands was a reflection of diminished synthesis of new hormone. Significant quantities of butanol extractable radioiodinated materials were found in the serum of each patient with active subacute thyroiditis indicating that despite the marked reduction in thyroidal uptake of $I^{131}$ some organic iodination presumably thyroidal was occurring In contrast with normal persons the butanol extractable $I^{131}$ concentration declined during the 24 72 hours after administration of radioiodine and despite marked reduction in uptake by the thyroid gland the absolute value of butanol extractable $I^{131}$ was normal or increased These findings probably indicate thyroidal synthesis of small amounts of iodinated materials which are rapidly released from the gland

The thyroid gland can maintain a large store of hormone which can supply hormone despite reduction or complete cessation of hormonal biosynthesis Release from the inflamed gland of abnormally large quantities of pre formed hormone and increase in circulating protein bound iodine result in hypermetabolism and thyrotoxicosis If synthesis is decreased stores become depleted and hypothyroidism ensues

X ray therapy to the gland was followed by rapid and complete return of normal thyroid function within a maximum of 4 weeks Cortisone was symptomatically effective but not as potent in restoring thyroid function to normal

It is suggested that during subacute thyroiditis two principal abnormalities in thyroid function occur diminution though not complete cessation of hormonal biosynthesis and loss of storage function of the gland with passage into the circulation of a variety of iodinated materials—proteins proteoses peptides and amino acids

**Persistent Thyroid Carcinoma** A characteristic of some thyroid cancers is slow rate of growth Although such tumors often can be held in check or temporarily cured by various forms of treatment persistence with recurrent symptoms after 5 or more years is relatively common hence *follow up for 10 and even 20 years is necessary* to evaluate thyroid carcinoma adequately William A Meissner and Merle A Legg[5] (New England Deaconess Hosp Boston) report 17 cases in which thyroid carcinoma persisted for

(5) J Cl n. E doc l. 18 91 98 J y 1958

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(6) J Cl E doc nol. 17 842 848 J ly 1957

normal adults In those with cretinism the titers of TSH varied widely from patient to patient being either undetectable or excessively high In 1 completely athyreotic cretin untreated for 11 years TSH activity was not demonstrable before therapy but after 6 months of therapy with thyroid hormone the TSH level was markedly elevated and was slightly lower after an additional 5 months of therapy Another aged 7 months had the highest serum TSH level thus far recorded while he was being inadequately treated with thyroid hormone Definite suppression was apparent after 2 months of therapy with a larger dose of thyroid but inhibition was still incomplete In the others TSH level was elevated before treatment and relatively short treatment with small doses of triiodothyronine resulted in complete disappearance of TSH from the blood

The complete lack of TSH in a severe case of cretinism which had been untreated followed by high levels after therapy with thyroid hormone is not unexpected Absence of pituitary acidophils has been noted in some species of animals after thyroidectomy Replacement with thyroxin maintains the acidophils and allows secretion of growth hormone and increase of body weight Moreover the pituitary gland and/or hypothalamic centers may suffer from the generalized suppression of metabolism while replacement therapy renews the ability to synthesize and release thyrotropin Before any final interpretation of the functional state of the pituitary in hypothyroid states is made it is important to measure the level of thyrotropic activity in the serum

**Therapeutic Concepts Relating to Hypothyroidism in Childhood** Donald E Pickering and Delbert A Fisher[7] (Univ of Oregon) emphasize the need of early diagnosis and adequate therapy in congenital hypothyroidism if potential central nervous system growth and development are to be realized Thyroid deficiency at birth which is sustained through early life produces irreversible histologic and functional changes in the central nervous system The brain is grossly deficient in weight has abnormal vasculature deficient myelinization and degenerative and atrophic changes of neuronal and interstitial components

In utero thyroid hormone deficiency is unlikely A normal placenta in an euthyroid mother transfers adequate thyroxin

(7) J Chron D 7 24 263 M b 1958

to maintain normal growth and development Athyroid infants have no apparent hormone deficiency until 1 3 weeks after birth The amount of hormone necessary to reverse major physical signs and return gross metabolism to nearly normal is inadequate to promote normal skeletal and central nervous system growth and development Unfortunately treatment of the athyroid infant is started with homeopathic doses of desiccated thyroid (1/10 to ¼ gr daily) with gradual increase of the dose at intervals This prolongs severe hypothyroidism for 3-6 months the period when growth and development of the central nervous system is normally maximal

The clinical signs and symptoms of thyroid deficiency in early infancy vary only in degree from those seen in older children Respiratory distress and frank cyanosis may be striking and the position of opisthotonus may be assumed to maintain an airway as myxedema of the tongue and para and retropharyngeal tissues develop The cry becomes hoarse and low pitched swallowing becomes progressively more difficult jaundice persists motor and psychologic achievements progress only slightly and reflexes are sluggish and diminished Dwarfing and infantile proportions and delayed dentition are late signs and indicate that a valuable period for treatment has been lost and that intelligence probably will be dulled No one symptom or combination of signs or symptoms leads to diagnosis Possible thyroid disease must be suspected if there are any features of depressed metabolism or growth

In a term infant lack of ossification of the distal femoral epiphysis and/or the proximal tibial epiphysis strongly suggests intrauterine hormone deficiency and placental dysfunction During the 1st year secondary centers of ossification in the foot hand and wrist should be studied in infants suspected of hypothyroidism Levels of protein bound iodine (PBI) under 6 μg/100 ml and of butanol extractable iodine (BEI) under 5 μg are considered abnormal In borderline cases if diagnosis is suspected therapeutic trial of optimal substitution therapy is indicated Radioiodine uptake studies are helpful but the amount given should be restricted to less than 0 5 μc during infancy and childhood

*Sodium l thyroxin and desiccated thyroid are equally satisfactory* in treating thyroid deficiency 0 1 mg sodium l

thyroxin is about equivalent to 90 mg desiccated thyroid From birth to 8 months 0 1-0 15 mg sodium l thyroxin/day is the average dose required to produce serum BEI values of 6 10 µg/100 ml whereas 0 15 0 2 is required between age 8 and 12 months In older children the dose is proportionally increased to an average of 0 3 mg/day by adolescence Toxic signs are rare with BEI values below 12 µg/100 ml The dose is adjusted to maintain serum BEI concentration at 6 µg or over as this induces the desired clinical and metabolic effects including normal growth and development of the skeletal and central nervous systems

► [The need for *adequate* treatment of hypothyroidism early in infancy is now well recognized Less well understood is the fact that the doses of thyroid required by infants are large Our feeling (like that of Pickering and Fisher) is that the only satisfactory criterion of adequate treatment is the blood PBI or BEI If one waits to evaluate treatment by growth curves or bone age the optimum time for treatment ha passed before the inadequacy of treatment is recognized Some of these problems have also been discussed in a Ross Pediatric Research Conference published in 1957 and available in reprint form from the Ross Laboratories Columbus Ohio —Ed ]

**Effect of Thyroid Therapy on Tone and Contractility of Urinary Bladder in Hypothyroidism** was studied in 3 patients by C J Mendez Bauer R Caldeyro Barcia R De Angelis J Maggiolo A Pou De Santiago and J C Mussio Fournier[8] (Montevideo Uruguay)

METHOD —Intravesical pressure is recorded by a water manometer connected to the vesical cavity by a catheter introduced through the urethra The manometer has a recording device which inscribes the vesical pressure on a kymograph

The record is begun with the bladder nearly empty (contents 20 cc ) The bladder continuously registers small rhythmic contractions 1 3 cm in amplitude Tone is the pressure exerted by the bladder between the contractions Intravesical injections of 50 100 cc sterile physiologic saline are made with a syringe through the catheter used for recording the intravesical pressure During each injection the record is interrupted by turning a three way stopcock After each injection contractility is recorded for 10 20 minutes to determine the influence of distention on vesical tone and on the amplitude of the contractions of the bladder The intravesical injections are continued until a pressing desire to micturate is felt by the patient At this moment the vesical distention curve is finished The vesical evacuation curve is then recorded during successive removals of 100 cc liquid at a time vesical contractility being registered for 10 20 minutes after each extraction

Treatment with desiccated thyroid had the same effect on bladder tone in the 3 patients studied Thyroid therapy de

(8) J Cl E d 1 17 884 888 J ly 1957

creased the distensibility of the bladder The total amount of fluid which could be injected into the bladder (before a pressing desire to micturate developed) was much greater before than after treatment For equivalent volumes bladder tone was much greater after treatment than before The intensity of the rhythmic contractions of the bladder underwent no significant change after treatment

The values found for the bladder tone in these hypothyroid patients after therapy were similar to those reported by Denny Brown and Robertson for normal persons As the values for vesical tone were lower before treatment it is evident that hypotonia of the bladder accompanies hypothyroidism This agrees with other reports concerning hypotonia of various viscera in hypothyroidism

**Homotransplantation of Thyroid Tissue in Identical Twins** G A von Harnack W Horst W Lenz and L Zukschwerdt[9] (Univ of Hamburg) studied a pair of identical twins whose mother had hypothyroidism during pregnancy In one the descent of the thyroid anlage had not occurred Radioiodine tests showed at the tongue base a small functionally insignificant amount of tissue which had stored $I^{131}$ whereas no activity was present over the normal site

At age 7½ years part of the thyroid of the healthy twin was transplanted to the other Without suture the implant was placed along either side of the trachea The donor continued to develop normally so that good regeneration of the thyroid can be assumed The hypothyroid twin required no administration of thyroid until 3 months after the transplant had *been made and then in smaller doses than pre*operatively A radioiodine test after 13 months showed that the implant was capable of taking up one fifth of the administered dose of iodine and was further capable of covering the necessary hormonal iodine needs for 10 20 days It is likely that in the future while supplying a basic amount of thyroid hormone internal production of the hormone will be sufficient to cover the changing requirements of increased physical and mental demands It is also possible that the implant will in the future increase in size

The occurrence of congenital hypothyroidism in twins is significant because it may give a clue to the etiologic importance of maternal *hormones or congenital disposition* If

(9) D tsch m d W h sch 83 549 555 Ap 4 1958

maternal hormones were the important factors, hypothyroidism should usually be a concordant finding in identical and fraternal twins. If, however, the congenital disposition were decisive, hypothyroidism should be concordant in identical twins and discordant in fraternal twins. The authors as well as others have observed hypothyroidism limited to one member of identical twins.

It has been shown that hereditary factors are insignificant in endemic cretinism. The incidence of hypothyroidism in the members of a twin set was about the same whether the twins were identical or fraternal.

The hypothyroidism of one member of the twin set studied by the authors cannot be explained either by the influence of maternal hormones or by congenital disposition.

[This is not likely to prove a practical method for treatment of hypothyroidism in most cases. However, when homotransplantation becomes practical, this may prove to be the ideal technic for treating insufficiency of the thyroid gland.—Ed.]

**Pretibial Myxedema Treated with Local Injection of Triiodothyronine** is described by Thomas A. Warthin and Burns R. Boshell[1] (VA Hosp., West Roxbury, Mass.). Pretibial myxedema has almost invariably been associated with exophthalmos and has been presumed to have the same etiology. Grossly, pretibial myxedema appears as firm brown or orange plaques located bilaterally, but not always symmetrically, on the lower anterior portion of the legs or dorsum of the feet. The advanced lesion may resemble brawny lymphedema. Microscopically, these lesions appear as classic myxedema with edema, fraying and homogenization of the connective tissue with large amounts of mucinous staining material deposited between the collagen bundles. No satisfactory explanation for its peculiar location nor its etiology has been found. Paradoxically, pretibial myxedema occurs only in persons who have hyperthyroidism and exophthalmos, are about to have it or are in remission. It may herald the onset of malignant exophthalmos.

Cortisone may help if the lesion is recent, but it has not been of value in patients who have had the disorder for over a year. Hyaluronidase, estrogens, thyroxin and iodine have been of little value. The authors injected 0.2-0.5 mg. triiodothyronine solution locally into an area of pretibial myxedema in a man who had had the lesion for over 10 years

(1) A.M.A. Arch. Int. Med. 100:319-321, Aug. 1957.

He also had malignant exophthalmos The lesion temporarily disappeared after the injections These results suggest that a local insensitivity to active thyroid hormone does exist for unknown reasons and that these are true areas of local hypothyroidism

**Production of Experimental Exophthalmos** in the fish Fundulus parvipinnis by administration of anterior pituitary preparations is reported by Robert Brunish[2] (Univ of California Los Angeles) Pituitary fractions were prepared from frozen beef pituitary glands obtained directly from local slaughter houses Commercial thyroid stimulating hormone (TSH) and ACTH were also tested The intercorneal distance of the test fish was measured with calipers to 0 1 mm before and after the intraperitoneal test injection The ratio of intercorneal distance 16 hours after injection to that before injection served as a measure of exophthalmos

During the acetone fractionation procedure the exophthalmic activity was not separated from TSH Pepsin treatment resulted in greater activity in fraction II than in fraction I whereas fraction I and commercial TSH had similar activities The pepsin treatment substantially reduced the TSH level and the level of pepsin inhibitor another substance closely associated with TSH Trypsin completely destroyed the exophthalmic activity of fraction I whereas 5 mg fraction II gave moderate and reproducible exophthalmos an average increase of 106% of the initial intercorneal distance Commercial ACTH at doses of 5 mg produced no exophthalmos and did not enhance the proptosis produced by simultaneous administration of commercial TSH or fraction II

Since it is pepsin stable the exophthalmic activity as measured in Fundulus parvipinnis appears to reside in a portion of the TSH molecule or as a separate entity There was no evidence that intact TSH is the active principal or that it is augmented by ACTH

The time course of exophthalmos and the concomitant chemical changes in the orbit showed a dip in the values for water content proptosis and hexosamine concentration at 4 8 hours followed by a rise in all 3 The mucopolysaccharide change probably governs the water balance and the water balance in turn regulates the degree of proptosis The

( ) E doc l gy 6 437 441 Ap l 1958

role of mucopolysaccharide in binding water is well known

Thyrotropin (TSH) has caused experimental proptosis in a variety of conditions Normal guinea pigs thyroidectomized guinea pigs few or many injections TSH alone or TSH augmented with other hormones have all been used These variable requirements have been attributed to contamination of TSH preparations by a specific hormone which causes the changes leading to exophthalmos The present experiments support this hypothesis

► [This paper offers further evidence to support the contention of Dobyns and Steelman (1954 55 YEAR BOOK p 576) that the exophthalmogenic factor is not identical with the thyrotropic hormone. This may help to explain the following observations—Ed ]

**Function of Thyroid in Euthyroid Patients with Exophthalmos** The BMR protein bound iodine (PBI) level and radioiodine uptake may be normal low or high in presence of severe exophthalmos To further study thyroid function in this disorder Thorkild Friis and Earle M Chapman[3] (Boston) measured the BMR PBI thyroid uptake of $I^{131}$ conversion to serum $PBI^{131}$ and paper chromatography of the serum after oral radioiodine in 8 clinically euthyroid patients with exophthalmos

The BMR 24 hour radioiodine uptake and PBI were normal in 4 the BMR slightly increased in 1 the PBI low in 1 and increased in 1 and the radioiodine uptake above normal in 1 The conversion ratio was increased (over 50%) in all and the $PBI^{131}$ was elevated in half the patients In the controls euthyroid patients without exophthalmos conversion ratios were under 40% in none was the $PBI^{131}$ elevated Paper chromatography revealed radioactive iodide and thyroxin in the serums of all 8 patients with exophthalmos Radioactive triiodothyronine was demonstrated in only 3 patients and appeared later than thyroxin

The results indicate that the thyroid tissue in patients with exophthalmos is overactive and producing a normal amount of hormone and suggest that storage of iodinated substances in the gland is lowered Usually normally iodinated thyronines are secreted

► [The fact that there is an exophthalmogenic factor in the pituitary has induced clinicians to recommend pituitary radiation hypophysectomy and other treatments directed toward the pituitary in an attempt to control the manifestations of malignant exophthalmos The following paper reports on several such treatments A similar paper by the same authors appeared in the *Annals of Internal Medicine* 48 445 1958—Ed ]

(3) Acta endoc n l 27 207 215 F b y 1958

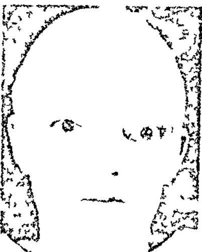
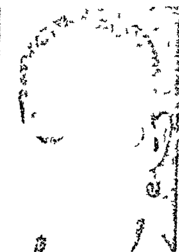
**Clinical Progress in Treatment of Exophthalmos of Graves Disease with Particular Reference to Effect of Pituitary Surgery** The exophthalmos of Graves disease is characterized by proptosis retraction of the eyelid and manifestations of increased bulk of periocular tissues caused by increases in amount of fat and of mucopolysaccharides and by edema The extraocular muscles are enlarged and infiltrated with fat and lymphocytes eventually becoming paralyzed and fibrosed Symptoms usually include burning pain lacrimation and diplopia

After control of the hyperthyroidism exophthalmos subsides in almost 60% of patients but not in the remaining 40% and it becomes extremely severe in 1% The exophthalmos is believed to be due to hypersecretion of thyroid stimulating hormone or a related exophthalmos producing substance Attempts at reducing exophthalmos except in orbital decompression are directed at suppression of pituitary hyperactivity E Perry McCullagh Marvin Clamen and W James Gardner[4] (Cleveland Clinic) report their experiences in 39 patients 9 of whom had hypophysial surgery

Roentgen irradiation to the pituitary region usually 2 000 4 000 r at the surface is of doubtful value Improvement is nil slight or variable Proptosis rarely decreases by more than 3 mm As much as 10 000 r has not produced measurable hypopituitarism and no detectable end organ response Therapy with desiccated thyroid or thyroxin has been unsuccessful improvement usually has been clinically insignificant or temporary Administration of ACTH 40 mg intravenously over a 6-hour period daily for 5 16 days and hydrocortisone in an initial dose of 200 mg orally daily and diminished over many weeks induced dramatic improvement in 10 patients

In some patients in whom nonsurgical methods have failed cauterization of the pituitary diminishes the exophthalmos Nine of the authors patients were treated by section of the pituitary stalk or cauterization of the anterior lobe or both When the stalk was sectioned an impervious diaphragm of waxed paper plastic or tantalum was placed above the sella turcica to prevent re establishment of the portal circulation In all exophthalmos improved in some disappearing almost entirely Visual acuity returned to normal

(4) J Cl E doc 1 17 1 7 1292 N mbe 19 7



laboratory tests and tests for function of the thyroid were normal

A right frontal craniotomy was performed and the anterior lobe of the pituitary cauterized the stalk divided and a piece of waxed paper placed between the divided ends of the stalk Improvement was noted within 5 days (Fig 108 *A*) with steady dramatic improvement for the next 2 weeks She then had an episode of polydipsia and polyuria alleviated with Pitressin® One month postoperatively she had a recurrence of active hyperthyroidism and the ocular signs became almost as severe as they had been before operation (Fig 108 *B*) The hyperthyroidism was controlled with Lugol s solution and then propylthiouracil Proptosis increased markedly but without associated periorbital edema (Fig 108 *C*)

Signs and symptoms of pituitary failure were pronounced 5 months after operation with fatigue amenorrhea intolerance of cold dry skin reduced body hair and severe hot flashes which disappeared when estrogen was given Nocturia and polyuria followed when Pitressin® was temporarily discontinued Ten months after operation she no longer required Pitressin and was asymptomatic Two and a half years later she felt well and had only minimal residual exophthalmos (Fig 108 *D*) She is maintained on desiccated thyroid 3 gr daily stilbestrol cyclically 1 mg daily and hydrocortisone 10 mg daily The BMR is −15% serum cholesterol 284 mg / 100 ml and thyroidal $I^{131}$ uptake 4% in 24 hours

► [The interruption of the hypothalamic hypophyseal connections as suggested above derives its justification from evidence that thyrotropic hormone secretion is controlled by the hypothalamus (see Harris Schweiz med Wchnschr 86 1252 1956 for a good summary in English) Unfortunately other types of pituitary tropic hormones are also controlled by similar mechanisms (see this YEAR BOOK p 631) Interruption of the pituitary stalk therefore usually causes amenorrhea and hypothyroidism and may reduce adrenal responsiveness Although the procedure is less traumatic than hypophysectomy it appears to have many of the functional disadvantages associated with the latter —Ed ]

► ↓ The pathogenesis of hyperthyroidism remains uncertain since some authors feel that it is a disease of the thyroid gland and others that it reflects hypersecretion of thyrotropin The next paper gives little support to the thyrotropic theory —Ed

**Hyperthyroidism in Patient with Postpartum Necrosis of Pituitary Case Report and Implications** are presented by Stefan S Fajans[5] (Univ of Michigan)

Woman 41 was first hospitalized at the author s institution in 1951 She had been weak for 15 years after severe uterine hemorrhage following a second delivery at home had caused unconsciousness She had been hospitalized for 9 weeks and had received blood transfusions She had not lactated after delivery menses had stopped and pubic and axillary hair had not regrown Intolerance to cold and lack of perspiration had developed The skin had become dry and he had become chronically constipated

Laboratory tests revealed mild anemia and leukopenia The BMR was 24% and pulse 48 Serum levels were as follows cholesterol 203

(5) J Cl E doc I 18 271 77 M h 1958

mg and fasting blood sugar 56 mg /100 ml and sodium 121 chloride 96 and potassium 5 1 mEq /L Urinary 17 ketosteroids were 0 4 mg /24 hours During a Robinson Kepler Power water test volume of overnight urine specimen was 224 ml and the 4 hourly urine volumes were 10 7 9 and 11 ml

Treatment was begun with 15 mg cortisone acetate, 3 5 Gm added sodium chloride and 32 and then 64 mg desiccated thyroid/day Appetite weight strength energy and well being increased When cortisone was increased to 20 mg /day nervousness insomnia and palpitation occurred During the next 2½ years therapy was changed to 25 mg hydrocortisone and 128 mg desiccated thyroid/day and 10 mg methyltestosterone buccally twice a day The patient then showed nervousness shakiness insomnia palpitation intolerance to heat and increase in perspiration She lost weight despite an excellent appetite Desiccated thyroid was to be reduced to 96 mg /day, but by error she increased it to 192 mg /day On examination 14 months later she showed tachycardia postural hypotension moist skin fine scalp hair finger tremor stare lid lag lagophthalmos and weakness of upper outer gaze and convergence Level of blood sugar was 35 mg and of protein bound iodine (PBI) 9 2 µg /100 ml After desiccated thyroid was stopped for 1 month BMR was 46% PBI 14 6 µg /100 ml and radioiodine uptake 54% Propylthiouracil readily controlled the symptoms which reappeared when it was stopped

Subtotal thyroidectomy revealed the gland to be much smaller than estimated clinically the 12 5 Gm resected represented about 80% of the total Microscopically there was advanced atrophy with only small focal areas of hyperplasia No circulating TSH was demonstrable before surgery Secondary adrenal hypofunction was demonstrated by rise in 17 ketosteroid excretion after ACTH administration The negative titers of urinary gonadotropins and low urinary excretion of estrogens indicated partial gonadal failure secondary to pituitary disease

Active hyperthyroidism developed and was maintained in this patient with postpartum necrosis of the pituitary The clinical biologic and pathologic evidence suggests that excessive secretion of pituitary thyrotropic hormone was not the cause

**Exacerbation of Hyperthyroidism by Methimazole during Iodide Therapy** was studied by Thaddeus E Prout and Samuel P Asper Jr [6] (Johns Hopkins Univ ) in 4 women treated for hyperthyroidism One was started on potassium iodide 5 drops 3 times daily 4 days later methimazole 15 mg every 8 hours was given The butanol extractable iodine (BEI) level and BMR gradually decreased throughout the treatment without exacerbation of the hyperthyroidism The second patient was given potassium iodide 20 drops 3 times

(6) A M A Arch Int. M d. 101 364 368 F b ary 1958

daily for 21 days whereupon the BEI level decreased from 12.6 to 2.7 µg/100 ml with a concomitant decrease in BMR and improvement in symptoms On the 21st day iodide was stopped and methimazole 20 mg every 8 hours started During the next 7 days the BEI and BMR increased and symptoms of nervousness and heat intolerance returned Methimazole was continued and symptoms abated as the BEI and BMR returned to normal A similar sequence was noted in the third patient In the fourth methimazole induced an exacerbation of hyperthyroidism despite the continuance of iodide

Release of thyroxin from the thyroid gland of patients with hyperthyroidism is stimulated by thyrotropin (TSH) and inhibited by iodide Discharge of thyroxin from the thyroid can be stimulated despite iodide suppression either by increasing the effect of the TSH or by decreasing the effect of the iodide Iodide appears to block thyroxin release effectively *in hyperthyroid patients although thyroxin pro*duction continues In the patients studied methimazole induced the release of thyroid hormone whether iodide was continued or not provided the iodide had been given sufficiently long The ensuing exacerbation was mild and transient and maximal 9 14 days after start of methimazole administration If TSH is given to patients with thyrotoxicosis under treatment with iodide the stimulation of the thyroid occurs within 24 hours suggesting that the release of thyrotropin induced by methimazole in the present patients did not result from reactivation of inactive thyrotropin already present The exact mechanism is unclear

► [This must be a very rare occurrence —Ed ]

**Effects of Radioactive Iodine on Maternal and Fetal Thyroid Function during Pregnancy** Radioiodine traverses the placental barrier of animals and humans Measurable doses of $I^{131}$ can be detected in the fetuses of mice sheep and bovines as well as humans after it is given to the mother The human fetal thyroid can accumulate demonstrable amounts of $I^{131}$ by the 12th week and its avidity for the radioactive material is much greater than that of the maternal thyroid gram for gram Offspring of women given $I^{131}$ during pregnancy may suffer radiologically induced damage to the thyroid gland with resultant hypothyroidism or cretinism Two

cases are reported by Keith P. Russell, Harvey Rose and Paul Starr[7] (Los Angeles).

CASE 1.—Woman, 33, had total thyroidectomy in May 1955 for papillary carcinoma of the thyroid, followed by deep x-ray therapy. Because of evidence of recurrence, she was given 225 mc. $I^{131}$ in August 1955. She was subsequently discovered to be 13 weeks pregnant at the time $I^{131}$ had been given. Protein-bound iodine at 6 months' gestation was 2 and at 8 months 3.8 µg. At term she delivered a 6 lb. girl who appeared grossly normal. At 5 days the infant's PBI level was 3.6 and at 5 weeks 1.7 µg. At 2 months the nose was flat and the tongue large. *Desiccated thyroid, ¼ gr., was started and was* rapidly increased to 1½ gr. daily, with subsequent rise in PBI to 5.8 µg.

CASE 2.—Woman, 35, had total thyroidectomy for papillary carcinoma in August 1954. She became pregnant in May 1955. At approximately 13 weeks' gestation she received 75 mc. $I^{131}$ for treatment of metastases. *At birth the infant girl weighed 6 lb. 7 oz. and appeared* grossly normal except for slight dryness of the skin, a small umbilical hernia and sluggish appetite. At 9 days the PBI was 1.4 µg. At 17 days l-thyroxin, 0.025 mg., was started and increased to 0.05 mg. The PBI went to 6.7 and then 5.7 µg. At age 12 weeks the infant acquired a respiratory infection and died. Autopsy revealed no thyroid tissue grossly or microscopically.

Large doses of $I^{131}$ given to the mother are hazardous to the fetus. Since these infants did not appear to be cretins, it appears they suffered from an acquired hypothyroidism from the 13th intrauterine week. Cretinism may be a more basic metabolic disturbance dating from conception.

To detect congenital hypothyroidism as early as possible, determination of the PBI in the cord blood may be valuable. Normally at term, maternal PBI averages 8.9 µg and that from concurrently taken cord blood is 7.7 µg. This test should be carried out in all suspect cases, such as those in which $I^{131}$ may have been given to the mother during pregnancy.

► [Obviously one would rarely have to give such large doses of radioactive iodine to a pregnant woman. It is not clear, however, that the unfortunate results were always a result of the $I^{131}$. In Case 1, for example, the patient was grossly hypothyroid during the course of her pregnancy. The deleterious effects of thyroid deficiency on the fetus are well known (Man, Shaver and Cooke: Am. J. Obst. & Gynec. 75:728, 1958). It may have been this factor rather than radioactive iodine treatment which produced infantile hypothyroidism. As previously mentioned, treatment of the infant should be energetic, and one may question whether maintaining the child at a PBI level of 5.8 µg./100 ml. is really adequate in view of the fact that the normal PBI at this age is much higher than for adults (see this YEAR BOOK, pp. 658 and 672).—Ed.]

(7) Surg., Gynec. & Obst. 104:560-564, May, 1957.

# DISORDERS OF CARBOHYDRATE METABOLISM

**Hereditary Fructose Intolerance Previously Unrecognized Congenital Metabolic Disturbance** was observed in 4 patients by E R Froesch A Prader A Labhart H W Stuber and H P Wolf[8] (Univ of Zurich) The disorder is distinguished from so called essential fructosuria by occurrence of hypoglycemia following ingestion of fructose which leads to excessive and prolonged rise of fructose concentration in the blood and to excretion in the urine of about 10% of the ingested fructose Concurrently blood glucose level falls as low as 10 mg /100 ml The severe hypoglycemia lasts for several hours with nausea hemorrhagic vomiting trembling profuse sweating and somnolence After acute symptoms subside slight transient hyperbilirubinemia and albuminuria may be noted

A girl aged 6½ and her brother aged 27 months had healthy parents and a normal sibling The other 2 patients were adult males related on the paternal side who had healthy children They had had severe symptoms during early childhood which had later gradually decreased A test showed decreased fructose tolerance in 1 Of 6 parents of the 4 who presumably carried the recessive gene of the abnormality 4 could be traced to the same ancestors in the 18th century Blood relation in the other 2 was probable as all came from the same village

Girl 6½ showed height (106 5 cm ) and weight (17 4 kg ) of a child aged 4½ years She had had frequent vomiting attacks during infancy which retarded growth At age 8 months the mother had recognized that vomiting often associated with sweating trembling and somnolence was related to ingestion of sugar Later the same symptoms were noted after fruits and carrots were taken Pure glucose and dextrin maltose mixture (nutromalt) were well tolerated Antipathy for sweets gradually developed and she began to grow satisfactorily only after all foods that she could not tolerate were excluded from the diet

Intelligence lagged somewhat behind chronologic age Aside from slight enlargement of the liver clinical findings were normal Glucose and galactose tests were normal All tests for fructose allergy were negative Paper chromatography showed a slightly increased urinary amino acid content Fructose tolerance was tested with 50

(8) S hw m d W b sch 87 1168 1171 S pt 14 19 7

Gm fructose/sq m body surface (Fig 109) After 40 minutes he became irritable began to sweat excessively was extremely pale and showed acrocyanosis Bloody vomiting ensued promptly Blood pressure of 115/65 before test rose in 4 hours to 135/85 After 6 hours she showed slight improvement but pallor acrocyanosis and somnolence persisted The following morning she was still nauseated and

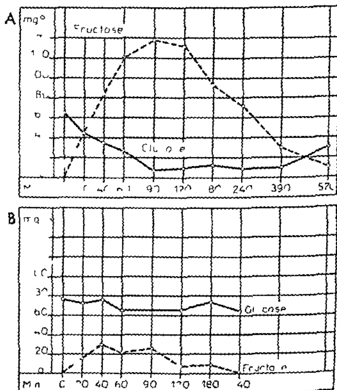



Fig 109 —Curve of fructose and glucose level in blood after ingestion of 50 Gm/sq m body surface A patient aged 6 with fructose intolerance B control aged 7 (Courtesy of Froesch E R et al Schweiz med Wchnschr 87 1168 1171 Sept 14 1957)

felt exhausted Slight icterus occurred 2 days after the test and lasted a few days without liver enlargement

Serum bilirubin level rose during this phase to 2 4 mg/100 ml and thymol turbidity to 6 5 units Urine showed transient albumin and a positive urobilinogen reaction With increase in the fructose level glucose level dropped the low point of 8 mg/100 ml was simultaneous with the fructose peak The severe hypoglycemia improved gradually after 9 hours when fructose had almost entirely disappeared from the blood 10% of administered fructose was excreted in the urine Leukocytes rose during the test from 6 500 to

27 000 whereas eosinopenia of 12/cu mm at the beginning of the test remained unchanged

The authors conclude that this disorder may be due to congenital absence of an enzyme responsible for one of the steps of fructose metabolism by the fructose 1 phosphate triose pathway

**Metabolism of Fructose in Man** In experimental diabetes in animals fructose was handled differently from glucose and did not require the use of insulin Max Miller James W Craig William R Drucker and Hiram Woodward Jr[9] (Western Reserve Univ ) studied the metabolism of fructose extensively

In normal persons the infusion of 1 Gm /kg /hour glucose caused an average maximum rise of 215 mg /100 ml in blood glucose above the normal levels With fructose the average rise in blood fructose above the control value was 77 mg /100 ml with only a slight rise in glucose (average 18 mg /100 ml ) Pyruvic acid levels in the blood rose an average of 28% after glucose infusion and almost four times this amount after fructose In the normal subject fructose is removed from the blood stream more than twice as fast as glucose during the period of infusion The rise in blood glucose after fructose administration indicates that a fraction of the fructose must have been converted to glucose the rise in pyruvate suggests that both glucose and fructose are metabolized by way of the Embden Meyerhof reactions Fructose is apparently transformed into liver and muscle glycogen by splitting to the triose state and entering the glycolytic scheme just below fructose 1 6 diphosphate

In the patient with diabetes mellitus who lacks adequate insulin the metabolism of fructose is almost the same as in normal subjects The rate of removal from the blood tream is almost the same pyruvate level rises to the same heights and serum inorganic phosphate falls rapidly In contrast in parallel circumstances glucose disappearance from the blood is markedly delayed pyruvate levels do not increase and decrease in phosphate is insignificant

The effects of fructose orally were compared with the same amounts of fructose intravenously in 3 diabetic patients The fructose was dissolved in water and ingested as a 10% solution In each instance the blood fructose level after

(9) Y I J B l & M d 29 335 360 Dec mber 1956

oral administration was lower than after intravenous infusion whereas blood *glucose increased* more than double and remained *higher for a longer period* Therefore part of the fructose *must* have been converted to *glucose in its passage* through the intestinal mucosa and *liver Consequently* the advantage of fructose *therapy* is somewhat diminished if *given orally*

Even in severe diabetic ketosis *the liver still takes up* fructose normally *This is an important* factor in the more rapid disappearance *of fructose from the blood stream* At least part of the greater peripheral concentration of pyruvic acid when fructose is *given is due to an increased output by* the liver Studies *of arterial and venous* concentrations suggest that muscle cells assimilate fructose directly without *the* presence of insulin In $C^{14}$ *labeled fructose* and *glucose* studies by measuring the *expired air after intravenous infusion* rapid *metabolic transport of fructose to* the CO pool is indicated without significant reduction in patients with diabetes even when insulin is absent The *oxidation of* fructose to carbon dioxide *does not seem to be under* the *control of* insulin

Carbohydrate *tolerance is altered* by trauma infection or starvation to a greater extent in patients with *diabetes mellitus* than in normal subjects *Under these circumstance* parenteral fluids are *often necessary* Accumulated *evidence* indicates that fructose *is the carbohydrate* of choice

*In diabetic* acidosis the patient is under stress either spontaneous or due to trauma *or infection* Insulin resistance is present and an *insulin antagonist has been demonstrated* repeatedly disappearing within hours of treatment Usually the patient is in carbohydrate starvation However glucose during the initial stages enhances the *cellular dehydration* and perpetuates the *polyuria Since fructose requires no insulin for its metabolism is more rapidly* removed from the blood stream and is a better *glycogen former than glucose* and since its *metabolism is not affected by* stress states or starvation there are *significant advantages to its use in* treatment of diabetic acidosis The rate of recovery is actually increased and contrary to *previous opinions* the increased production of pyruvic and lactic acids *does not have* a deleterious effect

**Hyperpyruvaturia Following Intravenous Administration of Fructose** Fructose is more assimilable than glucose and better metabolized in patients with diabetes Most studies have been on liver which metabolizes 30 50% of intra venously infused fructose V Hoenig[1] (Charles Univ Prague) with the technical assistance of J Hoenigova found that intravenous fructose increases the urinary excre tion of pyruvate mainly through changes of renal tubular activity Glucose does not do this

The hyperpyruvaturia is more pronounced than the ac companying increase in urinary inorganic phosphorus The results could be due either to an increase in the quantity of pyruvate filtered or to depression of tubular reabsorption The author s results suggest the latter since the average in crease in pyruvate filtered could not alone produce the hy perpyruvaturia observed and the condition was seen in some patients in whom there was a decrease in the filtered pyru vate The hyperpyruvaturia usually stops within an hour after administration of the fructose

Intravenous administration of fructose interferes with me tabolism of the renal tubules This leads to an increase in excretion of pyruvate inorganic phosphate and perhaps other metabolites The clinical importance of these observa tions is unknown

**Severe Diabetes with Remission Report of Case and Re view of Literature** is presented by Reed Harwood (Harvard Med School) Diabetic acidosis is generally believed to re sult from acute severe insulin insufficiency Patients who recover almost invariably need insulin injections for the rest of their lives Marked remissions are frequent in middle aged and obese patients with prolonged dietary restriction and weight reduction In rare cases the more severe insulin deficient diabetes of the young asthenic patient will go into remission after treatment by severe restriction of the diet or more usually by prompt and vigorous administration of insulin

Man 24 was referred because of rapidly progressive thirst poly uria and weakness which began 10 days earlier his weight dropped from 175 to 150 lb He appeared ill and weak and was markedly de hydrated He had 4+ glycosuria and acetone and 4+ albuminuria Blood sugar was 330 mg /100 ml serum carbon dioxide 8 5 mEq /L

(1) La t 1 506-508 M 8 1958
(2) N w E gl d J M d 257 257 61 A g 8 1957

pH 7 18 and nonprotein nitrogen 28 mg /100 ml During the next 9 hours he received 130 units of crystalline insulin and 4 L parenteral fluids Blood sugar fell to 53 mg /100 ml after 4 hours of treatment and the acidosis was quickly corrected He was regulated on a diet of 300 Gm carbohydrate 130 Gm protein and 120 Gm fat (2 800 calories) and was discharged on 80 units of lente insulin

For the next 3 months the urine remained sugar free and 5 p m blood sugar values ranged from 67 to 82 mg /100 ml The lente insulin was gradually reduced to 50 units When hypoglycemic attacks first appeared the insulin was further reduced to 25 units and then omitted The same diet was continued For the ensuing 23 months the patient has been well taking no insulin and repeated blood sugar values at 5 p m have ranged from 82 to 100 mg /100 ml Glucose tolerance tests however show the diabetic type of curve

The brief duration of the acute symptoms and the whole hearted co operation of the patient doubtless favored the recovery Few similar cases have been reported However *restoration of the function of the islands of Langerhans* in early diabetes is always possible Attempts to achieve this by the strictest control with diet and insulin should make such remissions more common

► [The literature regarding the new oral antidiabetic agents has grown immensely during the past year but no new light has been shed on the mechanisms of action of these substances or the indications for their use In view of continuing uncertainty as to how these medicines work I have *been sparing in my use of them At present I see no absolute indication* for their use although under certain circumstances their administration seems permissible I occasionally prescribe tolbutamide in patients who are responsive when clinical or social conditions make administration of insulin difficult (e g blindness or extensive travel away from home) There are however certain disadvantages to prolonged use of these drugs *In some* cases patients who have received tolbutamide for prolonged *periods* have developed late resistance to the medication This problem is discussed in the following paper taken from a most interesting symposium on these drugs (Deutsche med Wchnschr 82 1514 Sept 6 1957) —Ed ]

**Problem of Secondary Failure in Oral Treatment of Diabetes** was studied by E F Pfeiffer K Schöffling H Steigerwald G Treser and M Otto[3] (Univ of Frankfurt on the Main) in 54 cases *(7 1%) observed among 758* patients treated with tolbutamide Length of treatment varied to 20 months (in most patients 4-6 months) Other causes of treatment failure i e dietary violations operations or infections could not be elicited Of the 54 patients 41 had previously *been treated with insulin* Critical review of indications for oral treatment showed that all criteria had been fulfilled

Insulin requirement after successful *prolonged oral* therapy remained the same In the secondary failures the con

(3) Deutsche med. Wchnschr 82 1528 1531 Sept. 6 1957

ditions remained basically similar In a corresponding similar group of diabetics who had received only insulin for a prolonged period a significantly greater increase in insulin requirement developed than in those treated with the tablets Review of individual changes in exogenous insulin requirement after failure of oral treatment showed increase in 8 decrease in 3 and no change in the others In 2 patients with insulin requirement after secondary failure of oral therapy greatly increased no definite cause could be ascertained

The authors believe that secondary failure of oral treatment of diabetes is best explained on the basis of overloading of the decreased capacity of the beta cell system which delays appearance of resistance toward sulfonylureas As a rule this delayed disturbance of metabolism on oral therapy is transient without residual damage to the insulin producing islet cell system and measured by exogenous insulin requirement is less damaging than insulin therapy In individual patients however possibility of metabolic decompensation with prolonged oral therapy and of severe injury of islet function should be considered and controlled by timely termination of oral therapy

► [Toxic reactions have also been reported, including allergic dermatitis (Detusche med Wchnschr 83 100 1958) and photosensitization (ibid p 98) In both these cases and in all other instances of sensitization I am familiar with the drug in question was carbutamide (BZ 55) which is *not sold in the United States Tolbutamide appears so far to be a benign* medication

The fact that tolbutamide is not effective in about half of the patients with diabetes has spurred pharmacologist to seek another medication with wider applicability The results of one such study are outlined below Additional work with this substance has also been reported by Krall and *Gamerini Davalos (Proc Soc Exper Biol & Med 95 345 1957)* and Nielsen Swanson Tanner Williams and O Connell (A M A Arch Int Med 101 211 1958) In the latter paper the substance is referred to as PEDC All reports agree substantially with the following —Ed ]

**Clinical Report of New Hypoglycemic Agent** is presented by Julius Pomeranze Herley Fujiy and George T Mouratoff[4] (New York) In alloxan treated diabetic rats rabbits and Rhesus monkeys N β phenethylformamidinyliminourea (DBI) which is unrelated to the aryl sulfonylureas effectively lowered blood sugar levels A hypoglycemic effect was also demonstrated in normal animals The drug was then administered to 10 adults with diabetes mellitus and 1 with no disturbance of carbohydrate metabolism The subjects fasted overnight before each test and those with dia

(4) Proc Soc Exper Biol & Med 95 193 194 May 1957

betes were not given insulin on the morning of the test Each took 100 Gm glucose by mouth and blood samples were taken hourly for 6 hours The tests were repeated in the same subjects 1 week later but 100 mg DBI was given with the glucose

Blood sugar concentration decreased significantly in the normal subject and in the diabetics after ingestion of 100 mg of the drug The configuration of the glucose tolerance curve was altered after the drug was given This is unlike the action of sulfonylurea drugs which lower fasting blood sugar levels but do not alter the configuration of the glucose tolerance curve Blood sugar levels were effectively reduced within 3 hours of oral administration and the effect was maintained longer than 6 hours The effect was produced in patients with severe or mild diabetes mellitus in those in whom diabetes developed before age 40 and in those who had had the disease for more than 20 years

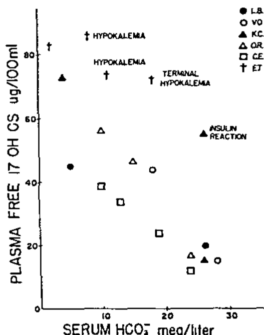
Nausea and vomiting occurred during the 4th hour in 1 patient and the experiment had to be terminated Blood glucose levels at this point were 80 mg /100 ml

**Adrenocortical Function in Diabetic Acidosis** *Adrenocorticosteroids are diabetogenic and ketogenic but their role in causing acute exacerbations of diabetes mellitus remains speculative* Stanley Wallach Edwin Englert Jr and Harold Brown (Univ of Utah) measured the free and conjugated 17 hydroxycorticosteroids (17 OHCS) in plasma and urine of patients with diabetic acidosis

Of the 6 patients 5 recovered from the acidosis All had elevated plasma free 17 OHCS at admission which in the 3 with uncomplicated courses returned to normal within 12 hours corresponding to the similarly rapid remission of the acidosis Two in whom hypoglycemia developed during insulin therapy had a delay in return to normal Plasma conjugated 17 OHCS measured in 3 were elevated 2-6 hours after admission All 5 had markedly elevated urinary excretion of 17 OHCS most of which was conjugated Excretion returned to normal 24 36 hours after admission In the patient who died the plasma free and conjugated 17 OHCS levels remained elevated until death This pattern was the result of continuing stress One patient had relative adrenocortical insufficiency

(5) M tabol m 6 107 115 M h 195

Increased adrenocortical activity was observed in all patients except the one with relative adrenocortical insufficiency The adrenocortical activity is comparable to that seen in patients whose acidosis is precipitated by stress The plasma free 17 OHCS is higher than in ordinary infection




Fg 110—R l t betw en pla m f 17 OHCS d rum b a bon t 6 p t ents w th deq t d enocort cal fu ( — 90) Each p t ent d t fied by liff ent ymbol S l dete m t on w pe f med d g t eatm nt Ob erv t on E T w t sed leul t g ) (C rt y f W lla b S *et l* M taboli m 6 107 115 M h 1957 )

or trauma These observations suggest that diabetic acidosis per se is a stressful situation capable of causing increases in adrenocortical activity

When the plasma free 17 OHCS levels and serum bicarbonate are correlated in patients without insulin hypoglycemia (Fig 110) a close relation is een The patient with relative adrenocortical insufficiency evinced a low level of adrenocortical activity before and during numerous episodes of diabetic keto is and mild acidosis Urinary excretion pat

terns are unreliable because of the discrepancies introduced when severe renal dysfunction is present

The data suggest that the increased adrenocortical activity seen in diabetic acidosis is a result and not a cause of the syndrome

**Role of Adrenal Cortex in Inhibitory Regulation of Insulin in Diabetes Mellitus** was studied by R Jaumann[6] (Univ of Zurich) by administering insulin tolerance tests to 8 diabetic patients Plasma 17 21 hydroxycorticoids were estimated before and 1 and 4 hours after administration of insulin Only 1 patien showed signs of hypoglycemia 2 hours after insulin injection with a blood sugar level of 53/100 ml hunger slight dizziness and sweating The patient recovered spontaneously in about 10 minutes so that interruption of the test by glucose injection was not necessary After another 2 hours at the end of the test blood sugar again was 125 mg and the patient felt completely well All other patients showed no objective or subjective signs of hypoglycemia With the one exception blood sugar curves in all tests were similar with the relatively largest decrease of blood sugar after 1 hour

Fasting value of 17 21 hydroxycorticosteroid in plasma was within normal range with an average of 16 µg % Blood corticoids showed two basically different types of curves In 5 patients increase after 1 hour averaged +63% the same tests in normals showed an increase of +42% In 3 diabetic patients no increase occurred No significant difference was noted between controlled and uncontrolled diabetics in blood sugar response and plasma 17 21 hydroxy corticoids

These findings demonstrate that in the diabetic a sudden drop of blood sugar due to insulin may stimulate the adrenal cortex even when hypoglycemia is not severe enough to cause symptoms However there was no indication that basal adrenal cortical activity is abnormally increased

**Studies on Insulin Antagonism in Plasma** by J Vallance Owen and F D W Lukens[7] (Univ of Pennsylvania) indicate that in certain types of insulin resistance the inhibitory mechanism is hormonal rather than immunologic Studies were done on normal depancreatized depancreatized adre

(6) Schw med Wschr 87 1069 1072 Aug 17 1957
( ) Endocr (l) gy 60 6 5 633 May 1957

nalectomized (Long Lukens) and depancreatized hypophysectomized (Houssay) cats with various hormone replacements Plasma insulin activity and insulin antagonism were estimated by a previously described method comparing the uptake of glucose by rat diaphragm from undiluted plasma with the uptake from a buffer solution with and without added insulin

The mean plasma insulin activity of normal cats was 114 µU/ml When insulin was added to the plasma in vitro there was essentially complete recovery of the added insulin effect demonstrating that there was no inhibition or antagonism to insulin Normal cats given daily doses of regular insulin for 2 weeks showed no insulin antagonism

Plasma from depancreatized cats showed considerable inhibition of insulin added in vitro The plasma of these animals permitted recovery of only 10 25% of added insulin i e a mean inhibition of added insulin of 85% Without added insulin there was no demonstrable insulin activity in *the plasma Depancreatized hypophysectomized cats showed* no insulin activity in the plasma but demonstrated no insulin antagonism permitting complete recovery of added insulin Treatment of these animals with growth hormone and cortisone did not cause return of insulin inhibition Depancreatized adrenalectomized cats showed no measurable insulin activity in the plasma and no insulin antagonism Treatment of these Long Lukens animals with cortisone or hydrocortisone for 4 days resulted in return of the insulin inhibition characteristic of the plasma though treatment for 2 days did not restore this inhibitory property Treatment of these animals with growth hormone did not restore the insulin antagonism

The inference from these studies is that the insulin antagonism found in depancreatized cats results from combined activity of the pituitary and adrenal cortical oxysteroids Preliminary experiments indicate that the inhibitor is a protein or protein bound substance which appears to reside in the alpha beta or gamma globulin fraction It is not a lipoprotein This is also apparently the case with the antagonism to insulin previously reported within plasma of uncontrolled insulin requiring diabetic patients

► [The material discussed above appears to be similar to a protein or polypeptide described by Field, Tietze and Stetten (J Clin. Invest 36 1588 1957) This material migrates in the electrophoretic field as an alpha

globulin is destroyed by chymotrypsin and antagonizes human as well as animal insulin It is not glucagon or growth hormone and the administration of growth hormone to human beings does not call forth its appearance in the plasma Further studies of the identity of the substance will be of interest —Ed ]

**Retinal Vitreous Hemorrhages and Cataract in Prediabetic States** were observed by L Paufique and P Guinet[8] (Lyons) in 13 patients 8 of whom had the hemorrhages

A healthy appearing American man 39 had had recurring retinal hemorrhages for 6 months when first seen in 1954 He had been examined in the best clinics in the United States and all clinical and laboratory findings were negative Ophthalmoscopic examination showed fine capillary hemorrhages distributed throughout both retinas there were no retinal exudates Fine dustlike hemorrhages were also present in the vitreous Although the picture suggested diabetic hemorrhagic retinitis clinical findings appeared to contradict this diagnosis Two factors merited attention obesity (108 kg ) and known diabetes in a cousin A glucose tolerance test showed an abnormal curve (113 190 240 123 83 93 93) with a trace of glycosuria the first hour

The patient followed a strict diet and received pituitary irradiation He lost 10 kg in 6 months and the retinal hemorrhages disappeared only a few vitreous opacities had not disappeared Two years after first admission the ocular lesions were completely cured and vision was normal the vitreous was clear A few yellowish tiny scars were scattered in both retinas His general health was excellent and the diet was being continued scrupulously A year later his condition remained the same

In 5 patients 27 51 with beginning cataracts glucose tolerance tests also yielded a prediabetic curve Although a causal relationship seems probable it remains to be proved by further studies

The authors conclude that when a retinal or retinal vitreous hemorrhage occurs without obvious cause or when a cataract appears in young adults glucose tolerance tests should be carried out to determine whether a prediabetic state is present In the cases studied the retinal lesions have appeared to be more amenable to treatment than are such complications in frank diabetes

**Role of Adrenal Cortex in Diabetic Retinopathy and Nephropathy** There is considerable indirect and circumstantial evidence that adrenal cortical hormones may be involved in the pathogenesis of these two complications Harold Rifkin Samuel Solomon and Seymour Lieberman[9] (New York) measured the total identifiable and individual urinary 17

(8) A occul 190 97 811 N mbe 1957
(9) D bet 7 9 14 Jan Feb 1958

ketosteroids total urinary 17 hydroxycorticosteroids individual urinary corticoids plasma 17 hydroxycorticosteroids and the variations produced in these indexes by exogenously administered ACTH To evaluate the catabolism of steroids radioactive hydrocortisone was given intravenously to several patients and the appearance of radioactivity in the urine determined

Excretion of total identifiable ketosteroids i e 11 desoxy plus 11 oxysteroids by patients with uncomplicated diabetes is normal whereas in diabetic retinopathy and nephropathy the excretion is relatively normal or low In contrast small quantities are excreted by nondiabetic patients with renal insufficiency The C 19 11 desoxymetabolites alone were excreted by patients with diabetes and capillary vascular disease and by patients with nondiabetic renal insufficiency in considerably smaller amounts than by normal persons or those with uncomplicated diabetes The C 19 11 oxymetabolites were excreted by all diabetics in lesser or normal amounts Plasma 17 hydroxycorticosteroid levels were normal Response to ACTH was normal in terms of plasma and urinary 17 hydroxycorticosteroids and urinary ketosteroids

These results indicate there is no adrenal cortical hyperfunction in patients with uncomplicated diabetes diabetic retinopathy and nephropathy Others have reported clinical improvement in the retinopathy and nephropathy following hypophysectomy and adrenalectomy This benefit may be totally unrelated to the role of the adrenal and pituitary glands in pathogenesis of the capillary vascular lesions

► [The complications of diabetes continue to present the main problem in managing pat ents with diabetes mell tus Since some of these complications may arise at a time when the diabetes is so m ld that t is asymptomatic (1956-57 YEAR BOOK p 680) some clin cians have come to feel that they represent disorders parallel to the diabetes but not caused by it The adrenal cortex a favorite wh pping boy in stre sful situations has often been blamed (*e g* Becker *et al* Diabetes 3 175 1954) The *preceding* paper seems to elim nate this possibility completely —Ed ]

**Nature of Diabetic (Kimmelstiel Wilson) Glomerulosclerosis** Matthew J G Lynch and Stanley S Raphael[1] (Sudbury Ontario) studied renal diabetic lesions in terms of glomerular capillary microaneurysm formation fat changes hyaline arteriolar sclerosis and hyaline glomerulosclerosis In all cases of diabetic nephropathy the nodular diffuse and

(1) D be es 6 488 497 N Dec 1957

exudative glomerular lesions gave the intense deep blue of iron porphyrin compounds with the benzidine and nadi stains An aneurysmal lesion was suggested in many instances Erythrocytes were seen in some lesions In the diffuse type of lesion continuity with the vascular tree of the glomerulus was obvious Some were suggestive of ruptured aneurysms and many peripheral hemoglobin positive lesions were seen pushing into and becoming adherent to Bowman s capsule Hemosiderin and/or small numbers of hemosiderin positive erythrocytes were frequently found in the exudative lesions Staining with oil red O was diffuse and of moderate intensity and often revealed numerous fine and medium sized lipid globules Typical Maltese cross birefringence was present in some of the lipid vacuoles

All three types of lesions nodular diffuse and exudative stained intensely This finding coupled with positive hemochromogen tests dithizone and Fischler staining established the fact that the lesions contained hemoglobin in free and diffuse form In addition many lesions contained both intact and fragmented erythrocytes By analogy with retinal lesions many lesions in the glomeruli are probably aneurysmal The fact that the fused mass of erythrocytes within some glomerular capillary loops in a case of thrombotic glomerulonephropathy stained intensely by the silver oxide technic suggests that the argyrophilia of Kimmelstiel Wilson lesions is due to their content of lysed red blood cells Serial sections in 2 cases of predominantly nodular type Kimmelstiel Wilson lesions showed that some typical nodules contained a central small lumen in which erythrocytes were occasionally seen These probably represented microaneurysms whose walls had become enormously thickened

Although the evidence is incomplete the origin of Kimmelstiel Wilson glomerulosclerosis probably lies in aneurysms within the glomeruli

**Neuropathies of Diabetes** are segregated by John F Sullivan (Tufts Univ ) into two distinct forms (1) classic symmetrical distal neuropathy and (2) asymmetrical predominantly motor neuropathy or radiculopathy *The two* are clinically and presumably pathologically different entities with contrasting onset and prognosis Asymmetrical

( ) Neurology 8 243 249 Ap 1 1958

motor neuropathy particularly may antedate the clinical evidence of diabetes

Of 42 patients 11 had symmetrical distal neuropathy and 6 both symmetrical distal and asymmetrical motor neuropathy Symmetrical distal neuropathy is insidious in onset and predominantly sensory It may remain mild and non incapacitating but in chronic or uncontrolled diabetes increasing disability may develop with weakness trophic changes painless bladder distention and atony impotence and nocturnal diarrhea Pupillary abnormalities simulating Argyll Robertson pupils are common

In 25 patients the neuropathy began with pain weakness and muscle wasting Sensory impairment was less prominent and variable The distribution of pain motor weakness and sensory loss suggested that spinal roots or peripheral nerves might be affected singly or in an asymmetrical pattern On admission 16 of the 25 were not known to be diabetic and fasting blood sugar levels were normal The neuropathy was the first evidence of diabetes in many and the disease was mild and readily controlled by diet alone

Symmetrical distal neuropathy occurs in diabetes which is inadequately controlled or of long duration whereas asymmetrical predominantly motor neuropathy is often the first evidence of mild diabetes and tends toward spontaneous recovery Its clinical features are consistent with a vascular etiology

► [Lundbaek (Acta med scandinav 158 447 1957) has described an interesting complication a peculiar stiffening of the hands associated with paresthesias and pain occurring in patients with diabetes of long standing He believes that the syndrome occurs as a result of impaired blood flow —Ed ]

**Diabetes Mellitus Complicated by Bacteremia Caused by Gram Negative Bacilli** Infection commonly complicates diabetes mellitus Usually the infection is in the skin respiratory tract or urinary tract Of 137 patients who had bacteremia due to gram negative bacilli 14 were found to have diabetes The findings in these 14 patients are presented by William J Martin John A Spittel Jr William M McConahey and Warren A Bennett[3] (Mayo Clinic and Found ) Patients were aged 32 86

Twelve were age 49 or older Nine were men The duration of diabetes was less than 1 year to 25 years All had fever

(3) A M A A h I t Med 100 214 0 A g t 1957

exudative glomerular lesions gave the intense deep blue of iron porphyrin compounds with the benzidine and nadi stains An aneurysmal lesion was suggested in many instances Erythrocytes were seen in some lesions In the diffuse type of lesion continuity with the vascular tree of the glomerulus was obvious Some were suggestive of ruptured aneurysms and many peripheral hemoglobin positive lesions were seen pushing into and becoming adherent to Bowman s capsule Hemosiderin and/or small numbers of hemosiderin positive erythrocytes were frequently found in the exudative lesions Staining with oil red O was diffuse and of moderate intensity and often revealed numerous fine and medium sized lipid globules Typical Maltese cross birefringence was present in some of the lipid vacuoles

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(2) Neurology 8 43 49 Jan 1958

nosis of diabetes Almost certainly a mild diabetes preceded onset of gangrene in these 60 patients The development of gangrene was independent of the clinical severity of the diabetes as judged by the amount of insulin required to control the latter Gangrene was the chief cause of death in a large percentage of patients and contributed to death in



F g 111 —Adva d hy l t on f j xt gl m l r gm t f ff t rt l long t l l t N t d ff t p ll y gl m l l H m t yl eo d d f m 250 (C rt y f P ll E T Am J Cl P th 28 27 6 J ly 1957 )

all In patients with diabetes gangrene was frequently a terminal complication of some other form of vascular disease

The medium sized and small renal arteries had advanced intimal atherosclerosis in 50% of the diabetic and 25% of the nondiabetic patients Most persons with long standing primary hypertension have subintimal accumulations of hyaline material in the afferent glomerular arterioles but this seldom extends into the glomeruli A thick layer of hyalin in the juxtaglomerular segment of the afferent arteriole is almost pathognomonic of diabetes A layer of hyalin in the efferent glomerular arteriole establishes the diagnosis of diabetes Only hyalinization of the juxtaglomerular segment of the afferent arteriole (Fig 111) is characteristic of diabetes and its degree and the presence of intercapillary glomerulosclerosis are closely related

and 10 had chills Diabetes was out of control at the time infection was detected in 2 patients

Of the 14 infections 12 were due to organisms of the coli aerogenes group and 2 to proteus Operation on or manipulation of the urinary tract preceded the bacteremia in half the patients cholecystectomy in 1 and appendectomy in another The urinary tract was the apparent portal of entry in 13 of the 14 infections Cultures of the urine showed the same kind of organisms as those isolated from the blood in 8 Two patients died during treatment of the bacteremia of serious renal disease which probably made recovery virtually impossible

Treatment of such infections should include a streptomycin compound and one of the tetracycline group To prevent such complications in patients with diabetes infections of the urinary tract should be treated vigorously and antibiotic prophylaxis is probably indicated during operations on or manipulations of the urinary tract

► [It is difficult to emphasize enough the importance of avoiding manipulation of the urinary tract Despite the most rigid precautions instrumentation of the urethra carries a grave risk I am a good deal less optimistic than the authors about the value of antibiotic prophylaxis which suppresses only the sensitive organisms leaving the murderous resistant types free to do their worst —Ed ]

**Atherosclerotic Gangrene of Lower Extremities in Diabetic and Nondiabetic Persons** E T Bell[4] (Univ of Minnesota) reviewed autopsy records of 59 733 persons who did not and 2 130 persons who did have diabetes at the time of death at age 20 or older Gangrene of the lower extremities did not occur in any person under age 40 and in only a few under 60 among those who did not have diabetes Three persons with diabetes below age 40 had gangrene and between ages 40 and 60 the incidence was 14% The data indicate that gangrene develops 53 times as often in diabetic as in nondiabetic men over 40 Below age 60 the ratio is 141 1 above 80 12 1 If a man under age 80 has atherosclerotic gangrene the chances are 2 1 he has diabetes Among women gangrene develops 71 times as often in those with diabetes as in those without If a woman has atherosclerotic gangrene the chances are greater than 4 1 she has diabetes

No definite relation could be established between the known duration of diabetes and development of gangrene In 60 persons gangrene was the first sign that led to diag

(4) Am J Cl P th 28 27 36 J ly 1957

# CALCIUM PHOSPHORUS AND THE PARATHYROID GLANDS

**Ultrafiltrable Calcium of Human Serum II Variations in Disease States and under Experimental Conditions** The total serum calcium is composed of two major fractions nondiffusible or protein bound calcium and diffusible or ultrafiltrable calcium The diffusible portion is predominantly ionic calcium It theoretically traverses capillary membranes in vivo and participates in metabolic processes at the cellular level In normal adults 60 70% of serum calcium is ultrafiltrable

A Raymond Terepka T Y Toribara and Priscilla A Dewey[6] (Univ of Rochester) determined the ultrafiltrability of serum calcium in persons with hyper and hypocalcemia before during and after parenteral administration of calcium citrate phosphate and parathyroid extract

The distribution of calcium in serum between ultrafiltrable and nonultrafiltrable forms is governed by a purely physical chemical process the mass action relationship $Ca^{++}$ + Protein ⇄ CaProteinate in hypercalcemia whether secondary to a disease or experimentally induced by administration of calcium or parathyroid extract Calcium added to serum in vivo increases the ultrafiltrate calcium and proportionately increases the protein bound calcium so the ratio remains constant The same relation is clearly demonstrated in vitro

The parathyroids are concerned with equilibrium between calcium in bone and extracellular fluid Once in the serum the calcium released from bone obeys the law of mass action in it reaction with serum proteins Hypoproteinemia with presumably normal parathyroid function is associated with a low total serum calcium a normal or near normal concentration and a high percentage of ultrafiltrable calcium The concentration of calcium in ultrafiltrates of serum is determined by the bone extracellular fluid calcium equilibrium whereas the total serum calcium and consequently the percentage of ultrafiltrable calcium is secondarily determined by mass law relationships in serum or plasma Total calcium

(6) J Cl I t 37 87 98 J y 1958

**Hypoglycemia Simulating Psychoses** Symptoms due to hypoglycemia have been erroneously diagnosed as idiopathic epilepsy acute alcoholism brain tumor anxiety neurosis hysteria or psychosis Central nervous system symptoms may include loss of consciousness confusion drowsiness and stupor amnesia clonic convulsions and tremors inability to speak properly purposeless movements in co ordination stillness negativism twitching incoherence and mental dulness

If blood sugar falls rapidly the predominant early symptoms are those of compensatory hyperepinephrinemia with sweating weakness hunger tachycardia and inward trembling If blood sugar falls slowly to low levels over many hours the manifestations are cerebral with headache visual disturbances mental confusion coma and convulsions If the decrease is rapid profound and persistent the two groups of symptoms tend to merge

Clinical evidence of hyperinsulinism does not usually appear until the blood sugar has fallen below 50 mg/100 ml Attacks characteristically occur while the patient is fasting and respond immediately to administration of glucose A case is reported by Gilles Lortie and Dean M Laird[5]

Woman 32 started having symptoms of emotional instability in July 1955 She had a transient episode of paralysis of the left arm, followed next day by a drunken staggering gait and difficulty carrying or holding objects These symptoms became progressively worse speech became thick and hesitant and within 2 months she was spending all day in bed refusing to speak eat or respond She was admitted to a general hospital and then transferred to the state hospital with a diagnosis of catatonic schizophrenia The fasting blood sugar was 42 45 44 and 53 mg/100 ml and intravenous glucose tolerance tests resulted in flat curves An adenoma of the pancreas was removed and the patient's medical and psychiatric status dramatically improved

Patients with organic disease of the pancreas may show symptoms simulating many functional and organic states Only if the possibility is considered will the correct diagnosis be made

► [There is nothing new about the fact that hypoglycemia can simulate psychosis but it is useful to be *reminded of this fact from* time to time *Pancreatic islet cell tumors are not the only causes of this syndrome* over enthusiastic and ill advised administration of insulin to diabetics can produce the same derangement There are other disadvantages of overinsulinization which are well presented by Gordon in an editorial (Wisconsin M J 56 449 1957) —Ed.]

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(5) New England J Med 256 1190 1192 June 20 1957

ous system cardiac arrhythmia generalized spasticity and fatal tonic clonic convulsions

CASE 1—Woman 32 had low serum magnesium concentrations before surgery for adenomatous hyperparathyroidism One week after surgery numbness and tingling in the hands and feet began Hoffmann's and Chvostek's signs and bilateral hyperactive tendon reflexes appeared An ECG was abnormal. Serum chloride potassium sodium carbon dioxide calcium and pH were normal but magnesium was low Ten Gm of 50% magnesium sulfate intramuscularly in divided doses of 2 Gm each relieved the paresthesia abnormal signs disappeared and the ECG and serum magnesium concentration became normal During the first 6 postoperative days urinary excretion of magnesium decreased to a fraction of the preoperative excretion

CASE 2—Boy 8 had a peculiar generalized nonrhythmic twitching involving most of his body 3 days before operation Chvostek's and Trousseau's signs were absent Serum calcium was 18 phosphorus 3 2 and magnesium 0.2 mg/100 ml Postoperatively the same movements were displayed Calcium salt therapy was ineffective On the 2d postoperative day 3 Gm of 50% magnesium sulfate intramuscularly was followed within 1 hour by cessation of abnormal motor activity Twitching recurred several times during the following 3 days and was relieved each time by the magnesium sulfate

Possibly Parathormone[8] which effects bone dissolution and a phosphate diuresis could reduce body magnesium stores Magnesium losses parallel those of calcium and phosphorus Hypomagnesemia and attendant symptoms should be observed oftener in hyperparathyroidism than is indicated by previous reports The clue to its presence may be the occurrence of tetany after surgical correction of hyperparathyroidism that is refractory to administration of large amounts of calcium

**Hypercalcemia Nephrocalcinosis and Reversible Renal Insufficiency Associated with Hyperthyroidism** are reported in 1 patient by Franklin H Epstein Lawrence R Freedman and Howard Levitin[8] (Yale Univ ) Hyperthyroidism is often associated with osteoporosis increased urinary excretion of calcium and accelerated turnover of calcium stores but is not usually considered in differential diagnosis of hypercalcemia

Man 25 for 6 months howed fatigue headache nervousness and intermittent vomiting with weight loss of 55 lb despite recent increase in appetite He had polydipsia and nocturia 2 3 times each night. He had a prominent stare and lid lag The thyroid gland was slightly and diffusely enlarged pulse was 132 and blood pressure 180/80 Protein bound iodine (PBI) was 9 7 µg and butanol

(8) New England J M 258 782 785 Ap 17 1958

in serum reflects the level necessary to maintain the concentration of ultrafiltrable or ionized calcium determined by the parathyroid controlled bone extracellular fluid equilibrium and serum mass law relationship

*The hypercalcemia of malignant disease* Boeck s *sarcoidosis* and vitamin D intoxication was associated with elevated concentrations of ultrafiltrable calcium whereas the percentage of the total which was ultrafiltrable was within the range for normal persons with normal serum proteins These *findings indicate that the calcium disturbance is also due to* a primary alteration in the bone extracellular fluid calcium equilibrium with secondary changes in the total serum calcium

Hypocalcemia was accompanied by normal or a high percentage *of ultrafiltrable calcium When normal the serum* proteins were usually normal When the percentage was high the serum proteins were usually low In renal disease a high percentage of ultrafiltrable calcium was almost invariable regardless of the level of serum proteins so *that the actual quantity of ultrafiltrable calcium approached normal* The amount of calcium bound to serum proteins appeared to be specifically altered This accounts for the clinical observations that tetany is infrequent in renal disease

Abnormalities in concentration *of ultrafiltrable calcium* indicate disturbances in the bone extracellular fluid calcium equilibrium whereas abnormalities in percentage of ultrafiltrable calcium (ratio of ultrafiltrable to total serum calcium) are related to altered calcium protein interrelationships *in serum*

**Primary Hyperparathyroidism Associated with Hypomagnesemia** was observed in 3 patients by James W Agna and Richard E Goldsmith[7] (Univ of Cincinnati) Each had adenomatous hyperparathyroidism proved by surgical exploration *Magnesium is unquestionably important in human metabolism* Occurring in the body in amounts up to 1 600 mEq it is found in fairly large quantities in bone It functions as a coenzyme is a major intracellular cation and is important in neuromuscular conduction for both cardiac and skeletal muscle *Magnesium deficiency in lower animals is manifested by* vasodilatation hyperirritability of the nerv

(7) New Engl d J Med 258 2 2 225 J n 30 1958

level was 28-37 mg/100 ml Anemia became more marked and treatment was started with 300 mg cortisone daily with repeated blood transfusions He improved during the next few weeks The appetite increased vomiting ceased and he gained weight and was able to get out of bed Serum calcium level became normal and alkaline phosphatase rose to 21 King Armstrong units Excretion of calcium and phosphate decreased. The clinical course subsequently deteriorated and he died.

At autopsy the kidneys showed pale cut surfaces with a narrow cortex with wedge-shaped nodules of infiltration involving both cortex and medulla, which were accumulations of large uniform round cells similar to those present in the marrow Calcium was deposited in the cortex and medulla but the glomeruli showed little change The parathyroid glands were normal

Hypercalcemia may accompany any neoplastic invasion of bone Absence of new bone formation and the consequent normal level of alkaline phosphatase in the serum are features of myelomatous invasion In this case the most likely cause of hypercalcemia with resulting anorexia abdominal pain vomiting polydipsia and polyuria was the continued and widespread leukemic invasion of bones The remission presumably induced by cortisone was accompanied by increase in alkaline phosphatase presumably because bone *destruction stopped and new bone was being formed*

► ↓ The excretion of copious amounts of dilute urine is a common finding in patients with hypercalcemia The following 2 papers explore the mechanisms involved.—Ed

**Polyuria in Hyperparathyroidism is characteristic** Frequently the urine volume is so great and the concentration so low that diabetes insipidus is suspected S I Cohen M G Fitzgerald P Fourman W J Griffiths and H E de Wardener[1] (London) studied 2 patients In both the urine was more dilute than their own plasma even after dehydration or the administration of Pitressin®

After the parathyroid tumors were removed the urine could be concentrated even though the glomerular filtration rate had not changed in 1 patient and had risen only to 38 ml/minute in the other This suggests that the continuous hypotonicity of urine before surgery was not due to impaired glomerular filtration but to disturbed tubular function The hypotonicity cannot be the result of an osmotic diuresis or of an increase in the quantity of solutes excreted It does not depend simply on concentration of serum calcium for the blood level has not always been high but may be related to

(1) Quart. J M d. 26 423-431 Octobe 1957

extractable iodine 9 2 μg /100 ml Radioiodine uptake was 64 5% in 24 hours confirming diagnosis of hyperthyroidism He had hyper calcemia with normal serum phosphorus and phosphatase levels Daily urine volume varied from 2 500 to 4 500 ml and he could not concentrate the urine more than 1 010 even after overnight dehydra tion and vasopressin The nonprotein nitrogen level was slightly elevated phenolsulfonphthalein excretion depressed and endogenous creatinine clearance about 1/3 normal

He received a therapeutic dose of radioiodine followed by 300 mg propylthiouracil daily for 3 months with rapid improvement in symp toms Serum calcium level and 24 hour excretion of calcium returned to normal and serum phosphorus became low and alkaline phos phatase elevated Creatinine clearance more than doubled During subtotal thyroidectomy 3 normal parathyroid glands were identified Antithyroid medication was discontinued and he remained euthy roid Percutaneous biopsy of the left kidney showed severe interstitial scarring with considerable nephrocalcinosis Renal function contin ued to improve gradually

The immediate and permanent disappearance of hypercal cemia after successful treatment of hyperthyroidism strongly suggests a causal relation Elevation of phosphatase and de pression of serum phosphorus levels probably resulted from intense osteoblastic activity and recalcification of previously osteoporotic bone

► [This case like 3 previously reported (1954 55 YEAR BOOK p 519) emphasizes the difficulty of the differential diagnosis of hypercalcemia The causes of hypercalcemia include sarcoidosis (1957 58 YEAR BOOK p 696) multiple myeloma vitamin D intoxication acute osteoporosis can cer (1957 58 YEAR BOOK p 697) and hyperthyroidism Still an additional cause is described below —Ed ]

**Hypercalcemia in Acute Leukemia** is rare C Mawdsley and R L Holman[9] (London) report a case in which many clinical features could be attributed to the raised serum cal cium level

Man 20 with left sided chest pain after trauma had anorexia nausea and vomiting X ray showed rib fracture He had a white blood cell count of 8 000 with 31% neutrophils 59% lymphocytes 1% monocytes and 9% eosinophils During the ensuing weeks the symp toms continued and he was often febrile in the evenings Two months later he showed laboratory evidence of renal insufficiency Anorexia and vomiting became severe and he had polydipsia and polyuria Lymph nodes liver and spleen were not enlarged He had several small yellow plaques near the limbus of each eye The peripheral blood contained 20% primitive cells and he had anemia and thrombo cytopenia Serum protein levels were normal and no Bence Jones protein could be detected in the urine Serum calcium level was con sistently raised to 17 24 mg /100 ml Serum levels of inorganic phos phate and alkaline phosphatase were normal Blood urea nitrogen

(9) Lancet 1 880 Jan 12 1957

The data indicate that increase or decrease in plasma calcium concentration promptly produces similar change in the salt excretion rate There was no evidence to suggest that the changes were mediated through changes in the glomerular filtration rate but it was suggested that change in the plasma calcium concentration and in the calcium ex cretion rate caused immediate and opposite change in the

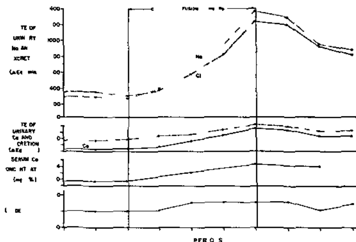



Fig 112—Eff t f l m f n o l f t l t lyt ex t cal m d ph ph ;l m ent t ma (C rt y f Le tt M F et I)

rate of tubular reabsorption of sodium and chloride The osmotic load of the calcium could not cause the salt diuresis because the induced salt diuresis averaged almost 20 times in total solute that due to the calcium per se Changes in urinary pH by acid or alkaline infusions did not appreciably alter the salt diuresis of a standard calcium load

**Observations on Hypoparathyroidism —I** *Exfoliative dermatitis as presenting sign of hypoparathyroidism case report* — A Harell Steinberg L Ziprkowski S Haim J Gafni and M Levin[3] (Tel Hashomer Israel) point out that idiopathic hypoparathyroidism has been known to cause trophic ecto dermal manifestations but only one report has recorded the occurrence of exfoliative dermatitis

Woman 35 had been under treatment for pulmonary tuberculo is

(3) J Cl E doc 1 17 1094 1098 S pt mb 1957

the high urinary excretion of calcium or to a direct effect of parathyroid hormone Both patients recovered from polyuria rapidly and in 1 the urine concentration had returned to nearly normal levels at a time when renal biopsy showed widespread deposits of calcium in and around the tubular cells

The fixed hypotonicity of the urine in hyperparathyroidism probably represents a failure of the second part of the distal and the collecting tubules to concentrate the hypotonic fluid from the first part of the tubules This loss of function is independent of the obvious structural damage to the kidney During osmotic diuresis the patients kidneys behaved like normal kidneys in the absence of antidiuretic hormone

**Effect of Abrupt Changes in Plasma Calcium Concentrations on Renal Function and Electrolyte Excretion in Man and Monkey** Patients with *hypercalcemia of diverse etiologies may show pronounced polyuria* often with considerable loss of urinary solute and severe depletion of extracellular salt and water This urinary wastage has been attributed to slowly developing pathologic changes *in renal tubules* produced by *prolonged hypercalciuria and nephrocalcinosis* However *renal response* may in part be conditioned by direct immediate physiologic *effect of the hypercalcemia* and/or hypercalciuria

This hypothesis was tested by *Marvin F Levitt Mark H Halpern Demetra P Polimeros Avron Y Sweet and Donald Gribetz* (Mount Sinai Hosp New York) *by infusing calcium gluconate or lactate 0 07 mg /minute/kg for 60-90 minutes*

During the *infusion* plasma calcium concentration rose promptly remained elevated throughout the *infusion* and afterward fell toward *normal* (Fig 112) *Plasma phosphoru*[s] *rose more slowly* No change was noted in plasma sodium potassium chloride bicarbonate or pH The rate of salt excretion *increased promptly during the 1st infusion pe*riod reached a peak toward the end of the infusion and persisted afterward Urine flow increased moderately but *there was no consistent change in potassium* When versenate was infused excretion rate of sodium and chloride decreased as plasma calcium concentration fell

(2) J Clin Invest 37 94 05 Feb u y 19 8

Ellsworth Howard test (200 units of Para thor mone® intravenously) mean phosphorus excretion rose from 14 2 mg to 25 2 mg/hour 13 2 to 20 2 and 38 5 to 46 mg/hour In a control subject in 1 patient with idiopathic hypoparathyroidism and in 1 with postoperative hypoparathyroidism rise in urinary phosphorus after 200 units of Para thor mone® intravenously was 200% 13 57 5 mg and 9 5 32 8 mg/hour respectively Thus the only evidence in favor of pseudohypoparathyroidism was the results of the Ellsworth Howard test on 2 occasions after an equivocal result on the 1st trial The parathyroid hormone was proved active because it induced rise of 342% in phosphorus excretion in the patient with postoperative hypoparathyroidism

The Ellsworth Howard test may be misleading If the target cells were refractory to parathyroid hormone skeletal changes should have been induced and the lack of deformities proved that at least during the years of maturation the target cells reacted well to parathyroid hormone When 200 units of Para thor mone® was incubated with the serum of a normal subject and injected into a normal subject rise in phosphorus excretion was the same as in the conventional Ellsworth Howard test When incubated in the serum of the patient with idiopathic hypoparathyroidism and injected into a healthy person no rise in phosphorus excretion was induced Similar results were obtained after incubation with the serum of another patient who had been resistant to Para thor mone® injections

Possibly there is a third acquired form of hypoparathyroidism in which neither the gland nor the target cells are pathologically involved Perhaps a substance in the blood can destroy the parathyroid hormone This evidence suggests that substances circulate in the patient s serum that can inactivate the parathyroid hormone

**Hypocalcemic Hypercalciuria during Vitamin D and Dihydrotachysterol Therapy of Hypoparathyroidism** *in 10 patients* suggested to Jorge Litvak Marc P Moldawer Anne P Forbes and Philip H Henneman[5] (Harvard Med School) a direct renal effect of these compounds Urinary calcium ordinarily varies with the level of serum calcium Patients with hypoparathyroidism characteristically present hypo

(5) J Clin. E docrin l. 18 246-252 M h 1958

for 2 years and for psoriasis for 1 year One month before admission she had been discharged from a sanatorium in stable condition but was readmitted because of acute toxic dermatitis She was toxic disoriented and had dyspnea and cyanosis There was generalized exfoliation of the skin which was erythematous swollen and wet. The hair was thin dry and sparse The mucous membranes were erythematous and swollen White blood cell count was 52 000 cu mm with marked shift to the left and 6-10% eosinophils Erythrocyte sedimentation rate was 105/123 serum protein concentration was low and albumin globulin ratio was reversed Serum calcium was 3 8 mg /100 ml Chvostek s sign was present All other electrolytes were normal.

The usual conservative treatment for generalized exfoliative dermatitis was to no avail Corticotropin and streptomycin were begun but the skin condition worsened and tetany became overt ACTH was then stopped She received 1 200 000 units of vitamin D by injection within 10 days Dihydrotachysterol (AT 10) was added on the 11th day (0 625 mg 3 times daily) and after 2 weeks was given alone After 11 days of combined treatment calcium level rose to 4 5 mg /100 ml 13 days later to 7 1 mg and by 40 days to 10 45 mg The general condition improved in parallel with clearing of the skin return of strength and disappearance of dyspnea After 5 weeks of AT 10 therapy the dose was gradually reduced then stopped Sixteen days later serum calcium fell to 6 9 mg /100 ml and the skin once more became swollen and erythematous Therapy with AT 10 was started again and within 10 days serum calcium rose to 9 1 mg /100 ml and the skin reverted to normal She was discharged in good condition receiving daily maintenance of 50 000 units of vitamin D

II *Inactivation of parathyroid hormone in case of clinical hypoparathyroidism*—Harell Steinberg and co workers[4] describe further observations on the patient reported

Two forms of clinical hypoparathyroidism usually are distinguished true idiopathic and pseudo In the pseudo form the defect seems to be in the target cells of the kidney and bones that are refractory to the parathyroid hormone The defect appears to be congenital and leads to disturbances in development that predominantly affect the skeleton The patients are short the metacarpal and metatarsal bones also are short but there often are pronounced differences in the length of the fingers and toes the neck is short the face round calcifications are present in basal ganglions and cataracts strabismus and other congenital malformations usually are present

None of these manifestations were present in the patient reported although the initial serum calcium level was 3 8 mg /100 ml When the patient was subjected 3 times to the

(4) J Clin. E docrinol. 17 1099 1104 Septembe 1957

**Metabolic Effects of 17 Ethyl 19 Nortestosterone in Man** Testosterone is widely used in treating osteoporosis and metastatic breast carcinoma Well being improves appetite and general strength return bone pain decreases weight is gained osteolytic lesions recalcify and soft tissue metastases shrink However hirsutism acne voice change and change in libido are disturbing side reactions The hypercalcemic syndrome occurs in 10 15% of patients with metastatic breast carcinoma treated with testosterone

Several testosterone derivatives were assayed in animals and 17 ethyl 19 nortestosterone was found to have the greatest separation of androgenic and anabolic effects Herta Spencer Eva Berger Martin L Charles Estelle D Gottesman and Daniel Laszlo[6] (Montefiore Hosp New York) administered this compound intramuscularly to 5 patients on controlled diets and studied the metabolic effects Two had senile osteoporosis 1 mild osteoporosis 1 carcinoma of nasopharynx and 1 pulmonary emphysema and fibrosis

A daily intramuscular dose of 25 mg for 18 days had no appreciable clinical or metabolic effect in 2 patients When the dose was increased to 50 mg urinary nitrogen phosphorus and potassium excretion decreased significantly on the first day and body weight gradually increased (Fig 113) Urinary calcium decreased slightly during treatment and the calcium tolerance test showed greater retention The nitrogen balance became positive

On 50 mg daily for 18-48 days patients appetite increased and a sense of well being persisted There were no signs of acne hirsutism or deepening of the voice and no fluid retention or changes in blood pressure pulse or temperature Signs of virilization were distinctly less than in patients receiving comparable doses of testosterone propionate over the same period None of the 5 patients had any evidence of major calcium loss before therapy therefore no marked improvement of calcium metabolism was expected Nevertheless there was a slight decrease of urinary calcium excre

(6) J Cl E do 1 17 975 984 A gu t 1957

calcemia and hypocalciuria before treatment but during treatment calcium excretion may be excessive despite low levels of fasting serum calcium Before therapy the expected hypocalcemia and hypocalciuria were present in the patients studied Vitamin D given alone dihydrotachysterol given alone or both given simultaneously resulted in hypercalciuria *although serum levels of calcium remained low* There was no obvious relation between serum phosphorus level and urinary calcium

Vitamin D and dihydrotachysterol raised the serum calcium level toward normal by increasing absorption of calcium from the gastrointestinal tract and by increasing bone reabsorption through increased urinary excretion of phosphorus Increased urinary calcium has been assumed to be *secondary to increased concentration of serum calcium* However urinary calcium could be increased to 500 mg *daily by a mere 3% reduction* in *tubular reabsorption* A direct effect of vitamin D and dihydrotachysterol on renal tubular reabsorption of calcium appears likely

In the past serum calcium levels were assumed to be satisfactory when the Sulkowitch test for urinary calcium was positive Presence of calcium in the urine does not necessarily imply normal levels in the serum A positive Sulkowitch test is not reliable for early detection of vitamin D or dihydrotachysterol overdosage Absence of tetany symptoms *is not a reliable indicator for absence of hypocalcemia* because many patients with chronic hypoparathyroidism can tolerate low blood calcium

Vitamin D and dihydrotachysterol apparently (1) increase absorption of calcium from the gastrointestinal tract and (2) increase bone reabsorption through increased urinary excretion of phosphorus (second action of vitamin D) A third action has been postulated increased intestinal absorption of nitrogen sodium potassium and magnesium The present data suggest a fourth action decreased tubular reabsorption of calcium

► {*In treating hypoparathyroidism one is caught between the* Scylla of tetany and hypocalcemic cataracts and the Charybdis of renal stone formation I try to keep the concentration of serum calcium in my patients at 8 5 9 mg /100 ml and instruct them to drink a good deal of water On this regimen most are *asymptomatic* and *(so far) stones have not been a problem* —Ed }

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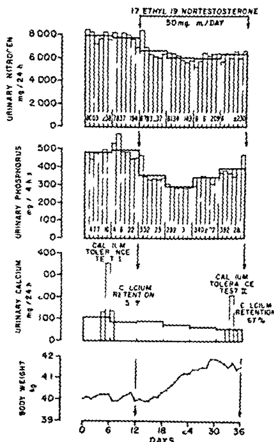



Fig 113 —Eff ct f 1 ethyl 19 nortesto t one on ur nary n t ogen, phosphoru and calcium x etion pat nt with senile osteopo os s. Narr w col m s epresent da ly u na y n t ogen ar d pho phorus excreti na. Averages with t nda d er f r respect e metabol c periods a e ente d at bottom f each g p of l m s and a e represented l y h y l n s n top (C urt y of Spencer H. t al J Clin. Endocrinol. 17 9 5-984 August, 1957 )

tion in each of the 3 patients who received the higher dose of 17 ethyl 19 nortestosterone

► [Other balance s udies have been reported by McSwinney and Prunty (J Endocrinol 16 28 1957) and others The fact that the anabo ic teroids also have progestational activity has led to their being tried for the treatment of certain types of infertility but with poor results (Rock, Garcia and Pincus Recent Prog Hormone Res 13 323 1957) Moreover there is eno gh androgenic activity in these compounds to raise the problem of masculinization not merely of the patient but of the fetus if given to women during pregnancy (Neilhaus New England J Med. 2 8 935 May 8 19 8) —Ed.]

**Prevention of Exudative Diathesis in Chicks by Factor 3 and Selenium** Factor 3 is a dietary agent preventing necrotic liver degeneration in the rat and degeneration of the heart liver kidney and muscle in the mouse It is an organic compound containing selenium Klaus Schwarz John G Bieri George M Briggs and Milton L Scott[7] showed that factor 3 preparations of different degrees of purity as well as selenium in organic and inorganic forms in doses similar to those which prevent liver necrosis in the rat prevented exudative diathesis in the chick

Necrotic liver degeneration was produced in the rat by a purified ration free from vitamin E and factor 3 This diet in chicks produced exudative diathesis inhibition of growth and death though the liver remained macroscopically normal The deficiency symptoms were prevented by adding tocopherol or brewers yeast to the diet Brewers yeast is free from vitamin F but contains factor 3 Other sources of factor 3 free from vitamin E were equally effective The protection in the chick could be predicted from the results obtained in factor 3 assay in the rat

The identity of factor 3 was established as the agent which prevented exudative diathesis in the chick Purified preparations of factor 3 contained organic selenium Sodium selenite prevented dietary liver degeneration in rats and prevented diathesis in the chick Selenocystathionine and elemental selenium were also effective

These results suggest that selenium may be a hitherto unrecognized essential trace element In the chick and rat selenium protects against serious and fatal deficiency syndromes at dose levels which are only a minute fraction of the minimal toxic dose The results are closely parallel between the rat and chick with respect to the protective effects of factor 3 and other selenium compounds under dietary conditions which lead to liver necrosis or to exudative diathesis respectively

► [The demonstration that selenium is an essential element in the diet of chick (simultaneou ly reported by Patterson Milstrey and Stokstad Proc Soc Exper Biol & Med 95 617 1957) and rats (J Am Chem Soc. 79 3292 1957) raises a question as to what its role may be in the human being Certa n parallels can be drawn between selen um deficiency syndromes in the rat and kwashiorkor however the importance of this possible relation hip remains to be determined—Ed.]

(7) P oc Soc. E pe B 1 & M d 95 621 6 5 A g Sept. 1957

**Environmental Temperature and Deprivation of Food and Water on Spontaneous Activity of Rats** Deprivation of food water or individual nutrients increases the spontaneous running activity in the rat Muscular activity is one way to maintain body temperature If the increased activity during starvation primarily reflects this attempt to maintain body temperature the degree of activity should be related to environmental temperature Such a relation was found by *J A F Stevenson* and *R H Rixon*[8] (Univ of Western Ontario) During 4 days of starvation the running activity progressively increased and the rate of increase depended on the surrounding temperature being greatest in the cold environments Spontaneous activity also increased markedly in the colder environments Refeeding resulted in an abrupt return to the initial level of activity or even slightly less and was characteristic of animals at all temperatures Complete water restriction produced a similar picture

Starvation increases the spontaneous activity of the rat and is related to maintenance of body temperature The body temperature tends to fall in starvation when activity is restricted but not when activity is permitted There seems to be little if any direct relation between the level of activity and the level of the basal metabolic rate in starvation Muscular activity appears to be closely related to the maintenance of body temperature and to be interrelated with food intake Increased activity on deprivation of water was also related to the amount of food eaten

**Physical Activity Performance and Attitudes of Group of Obese Women** are reported by *Ronald J Dorris* (State Univ of New York Syracuse) and *Albert J Stunkard*[9] (Cornell Univ ) in 15 cases Previous studies have focused on caloric intake of obese persons demonstrating that caloric excess is often due to excessive food intake but recently the factor of caloric expenditure has received increasing attention

Pedometer measurements indicated that the obese women walked less than half as much as the nonobese controls the weekly means being 14 4 and 34 4 miles About half the obese women estimated activity accurately but the others grossly overestimated activity More obese than nonobese

(8) Yale J B 1 & Med 29 575 584 J n 1957
(9) Am J M Sc 2 3 622 6 8 Jun 1957

women expressed a preference for sedentary activities Conversion of these findings into comparison of energy expended is difficult because the greater weight requires more work in performing most types of physical activity If translated into energy output the apparent marked difference in physical activity between the two groups may actually not be significant More adequate instruments are required for measurement of energy expenditure

Both the obese and nonobese women stated that they ate less when they were busy Obese women responded to despondency by passively accepting the depressive affects in striking contrast with nonobese controls who attempted to overcome them The same was true of feelings of boredom Thus the obese women showed attitudes that tended to diminish physical activity and they indicated difficulties in interpersonal functioning that tended to restrict social interaction

Physical activity of many obese women is so severely limited that even a modest increase might favorably alter caloric balance Developing insight on the part of the patient is no more effective than supportive or relationship therapy with the physician

**Cardiorespiratory Syndrome of Obesity** Glen A Lillington Milton W Anderson and Robert O Brandenburg[1] (Mayo Clinic and Found ) report 8 cases The triad of obesity alveolar hypoventilation with hypoxemia and secondary polycythemia in absence of intrinsic pulmonary disease has recently received *increased attention* The syndrome is characterized by extreme obesity cyanosis breathing irregularities congestive heart failure and a tendency toward excessive lethargy and somnolence Laboratory studies reveal absolute polycythemia pulmonary hypertension arterial hypoxemia and hypercapnia compensated respiratory acidosis alveolar hypoventilation and certain abnormalities in the ventilatory tests of pulmonary function Definitive evidence of primary pulmonary disease or a right to left cardiovascular shunt is lacking Appropriate reduction in weight reverses the clinical and laboratory signs of the syndrome

Obesity is considered the primary factor in development of this syndrome but the exact mechanism is not clear

(1) D Ch t 3 1 0 J ly 1957

Four obese patients had polycythemia and were free from intrinsic pulmonary or cardiac disease 3 obese patients with secondary polycythemia had definite bronchopulmonary disease of some form but obesity was the significant factor in the hypoxemia and 1 obese patient had no polycythemia but showed arterial oxygen desaturation on exercise

Woman 28 had dyspnea and cyanosis of recent onset. She had weighed over 350 lb for several years She had had excessive somnolence at times and recently was known to have hypertension and polycythemia She was 62 in tall and weighed 427 lb She was cyanotic dyspneic at rest lethargic and somewhat incoherent She had tachycardia blood pressure of 220/150 mm Hg and rapid shallow respirations with frequent short periods of apnea particularly when asleep

Laboratory tests showed albuminuria elevated blood urea nitrogen level hemoglobin value of 20 5 Gm /100 ml red blood cells 7 120 000 hematocrit value 76% normal white blood cell count total blood volume of 12 7 L and plasma volume of 3 L X ray showed cardiac enlargement with pulmonary vascular engorgement and an ECG showed right axis deviation Arterial oxygen saturation at room air varied from 70 to 90% but was 100% when oxygen was breathed The central venous pressure was increased and radial arterial blood pressure by direct measurement was 170/74

Treatment included removal of 2 870 cc blood by phlebotomy use of mercurial diuretics anticoagulants and weight reduction to 391 lb On discharge she was much improved with hemoglobin value 16 8 Gm and hematocrit value 64% In 6 months she was asymptomatic and weighed 251 lb All laboratory studies were normal A year later she weighed 135 lb and felt completely well

The immediate cause of the arterial hypoxemia appears to be alveolar hypoventilation The mechanical effects of extreme obesity may increase the work of breathing to the point that the respiratory centers maintain alveolar ventilation at a suboptimal level to decrease the work load Polycythemia is secondary There is no leukocytosis thrombocytosis myeloid immaturity or splenomegaly Arterial oxygen saturation is decreased The polycythemia corrects itself when the weight is reduced and arterial oxygen saturations return to normal

► [The reader is also directed to an excellent symposium on the use of intravenous fat emulsions for nutrition (Metabolism 6 591 November 1957) a comprehensive basic symposium on protein nutrition (Ann New York Acad. Sc 69 855 1958) and a symposium on obesity (Bull New York Acad. Med. 33 744 1957) —Ed.]

**Metabolism of Protein Moiety of Rabbit Serum Lipoproteins** Virtually all serum lipids are combined with proteins and are divided into two large groups—alpha or high density lipoproteins and beta or low density lipoproteins Each group may be further subdivided as to density lipid composition and N terminal groups of the proteins These various lipoproteins may have different functions suggested by changes in concentration following fat bleeding or heparin induced clearing Joel Avigan Howard A Eder and Daniel Steinberg (Nat l Inst of Health) studied the relative turnover rates and metabolic interrelations of the protein moieties of the major lipoprotein fractions using radiocarbon labeled protein injected into rabbits The protein moiety of the lipo*protein fractions turned over faster than the other plasma* proteins and the protein of the low density lipoproteins faster than the high density lipoproteins No evidence was found that lipoproteins with densities under 1 063 were significantly converted to those of greater densities or vice versa These results are consonant with previous studies showing that the proteins in these fractions have distinctly different chemical structure and physical properties and that they are metabolically distinct

► [One popular theory about lipid transport in blood has postulated that the protein portion of the lipoproteins acts as a carrier and that its characteristics on ultracentrifugation (i e whether it is high or low density) depend only on how much lipid is attached to the protein carrier The preceding paper demonstrates that the high and low-density proteins are different and not interconvertible. It does not however prove that the various classes of low density lipoproteins (< 1 0[illegible]1) may not have identical protein moieties—i e that the protein carrier of for example S 12 20 may be the same as the protein carrier for S 200-400 but the larger amount of lipid attached to the protein in the latter case may have lowered the specific gravity and therefore increased the flotation rate—Ed ]

**Influence of Dietary Fats on Serum Lipid Levels in Man** The precise chemical composition of ingested fatty acids in particular the degree of saturation may have considerable significance in both health and disease None of the experiments has proved conclusively that the effect of these dietary fats on serum lipids is due to the double bond structure of

(2) Proc. Soc. Exper Biol. & Med 95 4 9 433 July 1957

their fatty acids although this hypothesis has been widely accepted

Edward H Ahrens Jr William Insull Jr Rolf Blomstrand Jules Hirsch Theodore T Tsaltas and Malcolm L Peterson[3] (Rockefeller Inst) report their 3 year studies By oral feeding of liquid formulas closely supervised in a metabolic ward all variables were precisely controlled The feeding tests lasted 4-6 months and in 1 patient 36 continuous months without ill effect All patients had hypercholesteremia or hyperlipemia (some with clinical evidence of arteriosclerosis and xanthomatosis) or normal levels of cholesterol with arteriosclerotic heart disease

When all dietary fat was derived from corn oil the serum cholesterol decreased strikingly compared to the periods during which diet was ad libitum When coconut oil was substituted serum cholesterol again rose Serum levels were reproducible for each subject when corn oil was the source of fat An obvious difference between fats of animal and vegetable origin is the cholesterol present in the animal fats However the cholesterol depressing effect of corn oil is not due to the absence of cholesterol from that formula since adding cholesterol to the diet did not prevent the effect of the corn oil (Fig 114) Neither is the beta sitosterol content of corn oil responsible for its effect nor is there any appreciable change after removal of a large portion of the nonsaponifiable material

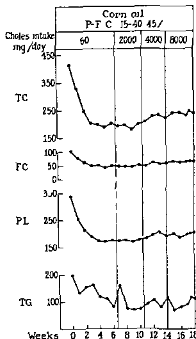
Thus three lines of investigation failed to show that the factors responsible for depressing serum lipid levels reside in the nonsaponifiable nonglyceride portion of corn oil The evidence suggests the glycerides themselves are responsible A roughly linear relation is seen when percentage differences in cholesterol or phospholipid levels are related to the iodine values of the fed fats (Fig 115)

It is important to learn whether the observed effects of dietary fats on serum lipids are caused by mean unsaturation or by the content of a specific unsaturated acid such as linoleic acid However the commonly occurring natural fats are so constituted that the total iodine value and linoleic acid content are largely interdependent

Serum lipids can be lowered by ingestion of unsaturated oils The major influence is exerted by the glycerides not

(3) La 1 1 943 933 May 11 1957

the nonsaponifiable fraction The lowest serum lipid levels were obtained when corn oil safflowerseed oil or cottonseed oil constituted the sole dietary fats All other fats tested resulted in higher levels and the differences were directly re lated to the degree of saturation of the glyceride fatty acids

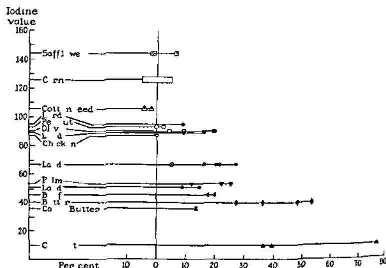



F 114—Effect m l p d f ddit s f h l te l to b co d f m la boy g d 13 C y t llin h l t l wa d l d w m co l d hom gen d n f mula I s h l t l d ph ph l p d l l t kes f 4 d 8 Gm /day w gn fi tly h gh (p<0 01) tha on 0 06 d 2 Gm /d y but d ff w mall (C rt y f Ab E H J t l La et 1 943 953 M y 11 1957 )

as measured by the iodine value Use of hydrogenated corn and cottonseed oils as sole dietary fats resulted in higher se rum lipid levels than when the corresponding unhydrogen ated oils were fed

*Neither the experiments reported here nor those reported* by others have ruled out the possibility that the responsible factors may lie in the nonglyceride portion of the fed fats Some authors have concluded that the effect of corn oil is due

to its sterol content Tests with molecularly distilled corn oils and reconstituted corn oil glycerides containing small amounts of nonsaponifiable material suggest that if a trace factor is involved it must be active in extremely low concentration Even after a sixfold decrease in nonsaponifiable material the corn oil retains its serum cholesterol depressing effect The critical experiments await feeding tests with



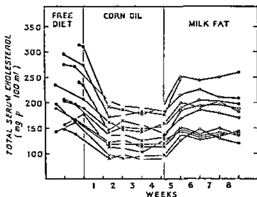

F g 115—Rel tion b tw en od l es of d tary fats a d rum ch l te ol l el xp e ed as p c tag d ffer fr m ba l t l l hed d g ge t n of o n oil. (Co te y of Ah ens E H J *t al* La t 1 943 953 May 11 1957)

glycerides synthesized from pure fatty acids The great cost of producing sufficient amounts of pure acids has delayed such experiments

Food habits should not be radically changed even in populations most seriously threatened by atherosclerosis Specific food factors which control serum lipid levels are not yet known When these mechanisms are understood practical measures for control of serum lipid concentrations will be available Only then can large scale epidemiologic experiments be planned to determine whether the incidence of atherosclerosis and its complications in the human species will be affected by decreasing the level of lipids in serum

**Effect on Serum Cholesterol of Diets Containing Different Fats** has been receiving increased attention in recent years Most investigators have done short term experiments on a few subjects Many used formula diets which were not physiologic Haqvin Malmros and Gerhard Wigand[4] (Univ of Lund) conducted 2 year experiments in healthy persons aged 18 61

From corn oil and other vegetable fats without altering the composition of the fats palatable products were produced resembling milk various cheeses and ice cream The basic




F g 116—I d d l lev l f t t l serum h l t l f 12 h lthy l t 1 t peri d l 2d p od m lk f t (C urt y f Malmr H and W g d G La t 2 1 7 July 6 1957 )

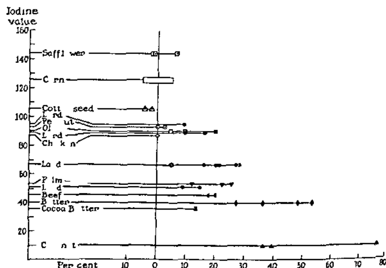
diet was bread cereals vegetables potatoes rice fruit and sugar to which were added various fats to be tested usually in amounts corresponding to 40% of the calories Vitamins A and D were given in adequate amounts The diet was varied and palatable and most patients adhered to it for months or years

When the ordinary free choice diet was replaced by the experimental diet containing fat only from corn oil the serum cholesterol fell promptly by about 70 mg/100 ml remained low for the 4 weeks of experiment and then increased after milk fat was reintroduced (Fig 116) During the feeding of corn oil the cholesterol remained low even when the subjects were fed 0 5 Gm cholesterol/day for 3 weeks

Hydrogenated coconut oil did not lower the original serum

(4) La cet 2 1 7 J ly 6 1957

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F g 115—R lat n bet een d val s f d t y f t d rum h lest l levels exp ess d per t g d ffe ce f m b l es estal l shed d n g a ge t of co n L (Court sy of Ah ens E H Jr *et al* La cet 1 943 953 M y 11 1957 )

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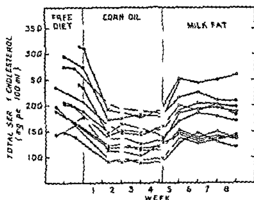



Fig 116 —Individual levels of total serum cholesterol of 12 healthy subjects during period milk fat (Courtesy of Malmros H and Wigand G Lancet 2 1 July 6 1957)

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Hydrogenated coconut oil did not lower the original serum

(4) Lancet 2 1 7 July 6 1937

levels of cholesterol Replacement of the coconut oil by equivalent amounts of corn oil produced a prompt fall When only one third the coconut oil was replaced by corn oil the serum cholesterol did not reach levels as low as those with corn oil alone

When the subjects were allowed a free choice supplemented by 50 Gm corn oil daily the serum cholesterol gradually rose However the corn oil diet could be supplemented with 100 Gm lean meat without raising the serum cholesterol from the low levels

Olive oil also depresses the blood cholesterol but not to the same extent as corn oil Rapeseed oil and safflowerseed oil have effects comparable to olive oil.

As to effect on the serum cholesterol there is no essential difference between vegetable and animal fat Most vegetable oils studied (corn olive rapeseed and safflowerseed oils) depress the blood cholesterol, but coconut oil does not Milk fat raises the serum cholesterol whereas whale oil depresses it The cholesterol-depressing effect of some oils apparently is related to the unsaturated fatty acids found in them in varying quantity

Milk fat and coconut fat contain only small amounts of linoleic acid and both tend to raise the cholesterol level Whale oil contains arachidonic acid which also is an essential fatty acid

Treatment with special diets containing 40% corn oil and 100 150 Gm daily of lean meat or fish in 19 patients with familial hypercholesterolemia lowered the serum cholesterol significantly in all but 1 None have died during treatment some still have angina pectoris attacks on physical exertion and the tendon xanthomas remain unchanged after a year of treatment

Replacing milk fat and other animal fat by corn oil produces a sharp drop in the serum cholesterol within a week and the low levels are maintained as long as the diet is maintained Since corn oil is available in a palatable form it is no longer difficult for patients to follow this diet indefinitely if indicated

► [The above two studies show that it is possible to obtain a sustained reduction of plasma cholesterol by dietary methods and that the effective agent in lowering the plasma lipids is not (1) a change in the cholesterol intake in the diet (2) an increase in sitosterol intake or (3) a material found in the nonsaponifiable fraction of the diet It therefore appears to be

a function of the triglyceride—and most likely the linoleic acid fraction of the triglyceride—components These conclusions are challenged in the next paper —Ed.]

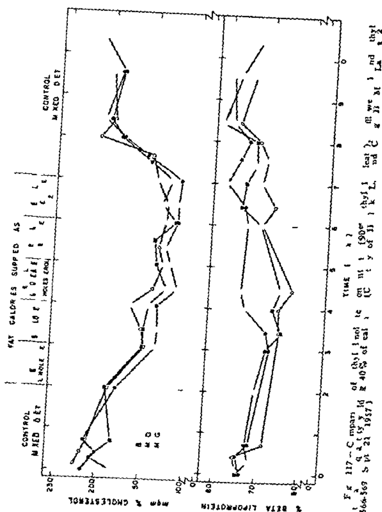
**Effect of Long Chain Polyunsaturated and Saturated Fatty Acids on Serum Lipids of Man** Blood lipids re pond to qualitative alterations in the intake of fats and oils Animal fats raise the serum cholesterol whereas vegetable and marine oils lower it This has been attributed to the long chain polyunsaturated fatty acids which are abundant in vegetable and marine oils Louis Horlick and B M Craig[5] compared the effects of corn oil safflower oil butterfat an ethyl linoleate concentrate obtained from safflower oil and ethyl stearate

Isocaloric exchange of corn oil for the mixed fats in the free diet resulted in a 20 30% decrease in serum cholesterol Corn oil yielding 54% of total calories lowered the serum cholesterol 20 30% and butterfat raised it 5 10% The cholesterol phospholipid ratio did not change appreciably with corn oil but the percentage carried as β lipoprotein decreased When ethyl linoleate concentrate was fed for 1 week then safflower oil for a 2d week and ethyl linoleate with 600 mg cholesterol daily for a 3d week (Fig 117) the cholesterol level fell stabilizing at 30-40% below control levels The ratio of free to total cholesterol and of cholesterol to phospholipid rose When ethyl stearate was substituted for ethyl linoleate the serum cholesterol did not change but the percentage of β lipoprotein rose to the control levels

When the diet was changed to contain no more than 10 Gm mixed fats daily yielding 4% of total calories the serum lipids decreased by 30-40% and decreased no further when ethyl linoleate was added and supplied 40% of the calories From the low levels attained on the low fat diet there was no discernible rise in blood chole terol with corn oil ethyl linoleate or ethyl stearate In fact with ethyl tearate there appeared to be a sustained fall

The results indicate that erum cholesterol could be reduced equally well by eliminating fat from the diet or by ingesting either corn oil or ethyl linoleate Ethyl linoleate had no special depressant effect on the serum cholesterol beyond that which could be observed by removal of fat from the diet These results do not support the concepts proposed

(5) Lancet 2 566-569 Sept 21 1957




by others that highly unsaturated fatty acids specifically depress the serum cholesterol

► [The fact that the substitution of ethyl stearate for ethyl linoleate did not raise the plasma lipid concentration is interpreted by the authors as indicating that the experimental depression of plasma lipids was not a result of feeding essential unsaturated fatty acids However this study suffers from a defect namely that the experimental periods were not very long The ethyl stearate experiment was carried on for only 1 week It may be unsafe to draw sweeping conclusions from such short term experiments in view of the different results obtained when longer periods of feeding were used, as described in the previous 2 papers —Ed.]

**Effect of Different Dietary Fats on Fecal End Products of Cholesterol Metabolism** Certain unsaturated fats have been shown to lower the serum cholesterol level in humans Because this effect might be due to increased excretion of the end products of cholesterol metabolism H Gordon B Lewis L Eales and J F Brock[6] (Univ of Cape Town) studied the quantitative changes in these end products during administration of different dietary fats

For 12 days 4 subjects were fed a basal diet containing 8 Gm fat and 2 000 calories Then the first 2 had 100 Gm hydrogenated coconut fat (iodine number 6) introduced isocalorically After 12 15 days this was replaced by 100 Gm sunflower seed oil (iodine number 135) for a similar period In the other 2 the dietary fats were introduced in the reverse order

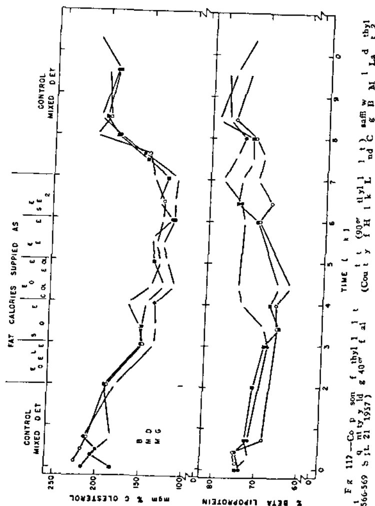
In 3 other subjects after 10 days of basal diet of 2 500 calories and 8 25 Gm fat 75 Gm hydrogenated coconut fat was added and after 10 days further supplemented by 75 Gm sunflower seed oil After 20 days the sunflower seed oil was withdrawn and only hydrogenated coconut fat supplement fed

In all 7 subjects when hydrogenated coconut fat was fed alone the serum cholesterol level rose When sunflower seed oil was fed before in addition to or after the fat serum cholesterol level fell Administration of either fat produced an increase in total fecal lipid somewhat more marked with sunflower seed oil than with the hydrogenated coconut fat The fecal neutral sterols were also increased when hydrogenated coconut fat was fed and further increased by sunflower seed oil Fecal bile acid excretion remained at basal levels when hydrogenated coconut fat was fed alone it almost doubled when sunflower seed oil was added

In these experiments therefore the fall in serum cholesterol induced by sunflower seed oil was associated with an increase in bile acid excretion consistent with the tentative hypothesis that in exerting its effect on serum cholesterol sunflower seed oil promotes the catabolism of this sterol and its excretion from the body

**Effect of Glucagon on Alimentary Lipemia** was studied by Margaret J Albrink James R Fitzgerald and Evelyn B Man[7] (Yale Univ ) to test the hypothesis that factors which

(6) N tu 2 923 924 N 2 1957
(7) P oc Soc. E pe B 1 & Med. 95 778 780 A g S pt 1957




by others that highly unsaturated fatty acids specifically depress the serum cholesterol

► [The fact that the substitution of ethyl stearate for ethyl linoleate did not raise the plasma lipid concentration is interpreted by the authors as indicating that the experimental depression of plasma lipids was not a result of feeding essential unsaturated fatty acids However this study suffers from a defect namely that the experimental periods were not very long The ethyl stearate experiment was carried on for only 1 week It may be unsafe to draw sweeping conclusions from such short term experiments in view of the different results obtained when longer periods of feeding were used as described in the previous 2 papers —Ed ]

referred for further information to an excellent Seminar on Atherosclero sis published in the *American Journal of Medicine* vol 33 at intervals during 1957 —Ed.]

**Effects of Alimentary Lipemia on Calcium Clotting Time of Human Plasma** When certain fatty acids are added to oxalated blood plasma the clotting time is accelerated as is whole blood clotting time after ingestion of 100 Gm olive oil or cream Such findings may be related to coronary dis ease Investigations were made by T R E Pilkington[8] (Univ of California) using the method described

METHOD—Blood was taken after a 10 hour fast and then every 1 1½ hours for 6 hours after ingestion of 180 ml cream The blood was taken by clean venipuncture with a 14 gauge needle after the first 5 ml had been discarded a sample was delivered through a plas tic tube into a lusteroid tube containing trisodium citrate It was centrifuged at 2 500 g and 0 C for 30 minutes after which the plasma was transferred to another lusteroid tube The calcium clotting time and chylomicron count were determined in each sample

In normal young adults a shortening of the calcium clot ting time usually occurred 1 2 hours after ingestion of cream coinciding with increasing lipemia The clotting time then lengthened even exceeding the fasting time at about 3 hours when the lipemia was maximal it then shortened again as the lipemia receded Shortening therefore occurred both be fore and after the height of the lipemia

When the subnatant chylomicron free fraction of the plas ma was tested calcium clotting times were appreciably long er than fasting time After cream ingestion the fraction showed no variation in clotting time The accelerating fac tor apparently was removed with the chylomicrons

After fat is fed to older persons the chylomicrons increase later and remain numerous longer than in young persons Because of this delay changes in clotting time occurred later and lasted longer in the older age group than in young sub jects

Previous work has shown unsaturated fatty acids do not shorten the calcium clotting time Investigation of the effects of olive oil *showed no lengthening of the clotting time but* since the lipemia obtained was only moderate no conclusions can be drawn The shortening of clotting time demonstrated in vivo in this study can be duplicated in vitro by stearic acid in concentrations of 0 002 0 01 mEq /L The small amounts of free fatty acid attached *to chylomicrons may be responsi*

(8) Cl Sc 16 261 68 M y 1957

*stimulate carbohydrate metabolism might reduce the degree* of alimentary lipemia Glucagon like glucose causes hyperglycemia and increased peripheral uptake of glucose as great as or greater than that caused by glucose The subjects were 6 healthy men A fasting morning blood sample was drawn and each man ate a test meal of 22 Gm protein 60 Gm fat and 42 Gm carbohydrate Another blood sample was taken 2 hours later and 0 03 mg glucagon/kg body weight was injected intravenously after which further blood samples were taken

Serum cholesterol and lipid phosphorus fractions did not *change appreciably In 4 subjects glucagon* caused an 18 24% increase in blood sugar and reduction in serum triglycerides The triglycerides had risen from a mean fasting level of 4 1 to 7 4 mEq /L at the time of glucagon injection and decreased an average of 1 8 mEq /L *½ hour later In contrast* intravenous injection of saline alone was followed by further rise in triglyceride concentration

The physiologic influence of glucagon on carbohydrate metabolism is similar to that of glucose By mobilization of liver glycogen it causes a temporary rise in blood sugar concentration It does not interfere with peripheral uptake of glucose and may even cause a greater peripheral uptake than does a hyperglycemia of similar degree evoked by intravenous glucose Glucagon also diminishes alimentary lipemia and decreases the concentration of plasma nonesterified *fatty acids These effects are identical with those of glucose* administration on alimentary lipemia the nonesterified fatty acids during fasting or after a fat meal The similar action of glucose and glucagon on lipid metabolism supports the view *that glucagon increases rather than inhibits peripheral glu*cose utilization The effect of glucagon on serum lipids is secondary to its hyperglycemic effect

► [The importance of a sustained carbohydrate catabolism in modifying *the concentration and clearing of plasma triglycerides* is also reflected in the ability of insulin to decrease and of epinephrine to increase the release of fatty acids from adipose tissue in vitro (Gordon and Cherkes Proc Soc. Exper *Biol. & Med* 97 150 1958) *and the fact that insulin promotes the* clearing of emulsified fat from dog plasma (Waddel and Geyer *ibid* 96 251 1957 )

The medical and experimental literature pertaining to lipid metabolism has grown so huge of late that it is impossible to cover the entire field completely in the small space available in the YEAR BOOK Readers are

do not combine with or yield hydrogen ions Anions are theoretically bases but some e g chloride and sulfate exhibit so little tendency to combine with hydrogen ions at body pH that they are completely ineffective as bases Protein ions are amphoteric under physiologic conditions some tend to donate hydrogen ions others tend to accept them

The main acids and bases in the body fluids important in regulating pH are bicarbonate phosphate and protein *Physiologic acid base balance can then be considered in terms of* hydrogen ions The fall in body pH in chronic diarrhea results from loss of fluid which contains relatively more bicarbonate than exists in body fluids Since the bicarbonate is formed from the dissociation of carbonic acid hydrogen ions are left behind in the body to produce acidosis Certain ammonium salts are acidifying because the ammonium ion breaks down into ammonia (which is metabolized by the body) and hydrogen ions which remain the extracellular fluid Lactate and citrate cause alkalization because they accept hydrogen ions and are then metabolized thus reducing the amount of hydrogen ion in the body

Since many acids and bases in body fluids are either anions or cations *disorders of acid base balance are usually associated* with disturbances in ionic pattern Clinical thinking has often equated changes in plasma bicarbonate with changes in pH so that high plasma bicarbonate concentrations have been considered indicative of alkalosis and low concentrations with acidosis However in uncompensated respiratory failure acidosis (i e low plasma pH) is accompanied by a high bicarbonate concentration because the increased plasma carbonic acid releases increased quantities of *hydrogen ion into the plasma In hyperventilation low plasma* pH is associated with low plasma bicarbonate

The association of elevated bicarbonate with low pH is a source of confusion unless the terms acidosis and alkalosis are used strictly to define conditions in which the blood pH is lower and higher respectively than normal The blood bicarbonate should be described simply in terms of its concentration

**Extracellular Hyperosmolarity Secondary to High Protein** *Nasogastric Tube Feeding is reported by* William S Wilson and John K Meinert[1] (Univ of Michigan)

(1) A I t M d 47 585 590 Sept mber 1957

ble for acceleration of clotting The much larger amounts of free fatty acid in the subnatant fraction presumably at tached to albumin are inactive in plasma clotting

This hypothesis is supported by the lack of shortening of clotting time when cream is fed to patients with xanthoma tuberosum and hyperlipemia who metabolize triglycerides to free fatty acids slowly Those with xanthoma tendinosum who utilize triglycerides normally showed the normal accel eration of clotting time after taking cream

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## ELECTROLYTES

► ↓ The innate conservatism of medical men has perpetuated a confusing and illogical nomenclature in regard to acid base balance Each generation of chemically trained medical students finds it necessary to unlearn all of its previous understanding in order to comprehend the jargon of the clinician A valiant attempt has been under way in the past few years to persuade medical writers to think chemically in regard to acid bas nomenclature The following abstract summarizes the chemists position A similar discussion was also presented by Relman (Am J Med 17 435 1954) —Ed

**Towards the Better Understanding of Physiologic Acid Base Balance** Disorders of acid base balance occur in many clinical conditions Much confusion has resulted from the arbitrary use of certain terms particularly acid and base and to a lesser extent acidosis and alkalosis *J A Owen*[9] (Univ of Melbourne) points out that these terms have di ferent meanings in chemistry and in medicine and that they should be used only in accordance with the accepted chemical definitions

In chemistry an acid is defined as a substance which yields hydrogen ions and a base a base combines with hydrogen ions to form an acid Examples of acids are car bonic lactic bisulfate ion and ammonium ion each of which gives up a hydrogen ion to form its respective base—bicarbo nate ion lactate ion sulfate ion and ammonia The electric charge on an ion provides no indication of its acidic or basic character Some substances can donate or accept hydrogen ions and act either as acid or base according to the pH of the solution When these definitions are applied to the compo nents of body fluids it is clear that the ions of metals such as sodium or potassium are neither bases nor acids because they

(9) M J Australia 1 327 328 M r 8 1958.

sodium body potassium became progressively depleted and the maximal urinary concentration decreased

The nephrons were isolated by microdissection after maceration in HCl and then stained with iron hematoxylin The characteristic structural changes were established by the end of the 1st week of potassium restriction and fully developed by 2 weeks At 2 weeks the kidneys were grossly normal in size and color at 3-4 weeks they appeared swollen with surface roughened Routine histology showed the outer zone of the medulla to be clearly outlined by the dilatation and enlargement of collecting tubules The clear epithelium of the collecting tubules was greatly swollen so that some cells protruded into the tubule lumen The original single layer of cells was replaced by masses of irregular cells which encroached on the lumen Mitoses were frequent

The lesion appeared to be that of excessive hydration of the cell protoplasm with cellular damage followed by hyperplastic proliferation In many cases the cells had ruptured (Figs 118 and 120) In normal collecting tubules the intercalated cells are insignificant but in the tubules of potassium depleted animals they stood out plainly in great numbers as deeply stained cells crowded between the clear cells or protruding in long bulbous projections into the lumen of the tubule (Fig 118) Tangential sections through the base of the epithelium (Figs 119 and 121) showed an alternation of intercalated cells with the swollen clear cells

The collecting tubules in the inner zone of the medulla were essentially normal from the ducts of Bellini to the junction with the outer zone At the junction of the inner and outer zones swelling and proliferation of the epithelium of the collecting tubules began abruptly and extended in decreasing intensity toward the cortex The result was a greatly thickened but not markedly distorted segment of tubule in which the increase in size and number of cells both clear and intercalated encroached on and at times obliterated the lumen The broad ascending limbs of Henle s loop were normal The distal tubule the region beyond the proximal *convolution had undergone no change except passive distention This distention is explicable as due to the demon*strated structural impedance to the flow of tubular fluid from

Man 50 had cardiospasm and chronic inflammation at the cardia, treated with multiple esophageal dilatations Because of continuing dysphagia he was started on high protein nasogastric tube feedings. Initial serum electrolyte concentrations were normal After 8 days of tube feeding (210 Gm protein 2,000 ml water 83 mEq sodium 1/9 mEq potassium) the serum sodium was 159 potassium 5 1 CO 21 and chlorides 134 mEq /L and nonprotein nitrogen was 159 mg /100 ml His clinical condition deteriorated markedly When appropriate therapy was instituted—mainly more water—the clinical condition promptly improved and electrolyte concentrations returned to normal

The major cause of the negative water balance was the increased renal solute load secondary to the protein intake of approximately 210 Gm daily This developed despite the daily intake of approximately 2 000 ml water The solute load was further increased by the liberal amounts of sodium and potassium included in the tube feeding The negative water balance occurred because there is a limit to the concentrating power of the kidneys and there is a minimal obligatory water loss with each unit of solute excreted

Patients on high protein nasogastric tube feedings must have adequate and sometimes large amounts of water to balance the high obligatory renal water loss associated with the increased renal nitrogen excretion secondary to the high protein intake Hyperosmolarity may be easily prevented by lowering the ratio of protein to water in the formula High protein feeding is well tolerated if enough water is supplied Once hyperosmolarity develops it is as easily treated as prevented Large amounts of fluid without sodium are required the exact amount is indicated by serial determinations of blood electrolytes urinary specific gravity and clinical response of the patient

► [There is nothing new about the preceding observations but it seems worth while to keep this important complication of tube feeding before the eyes of the medical profession —Ed ]

**Renal Lesions of Electrolyte Imbalance I Structural Alterations in Potassium Depleted Rats** Renal lesions have been described in experimental animals and clinical states in which electrolyte balance has been disturbed by prolonged diarrhea or vomiting but the nature and location of the lesion have been a matter of disagreement Jean Oliver Muriel MacDowell L G Welt M A Holliday W Hollander Jr R W Winters T F Williams and W E Segar[2] induced renal lesions in rats by feeding diets deficient in various electrolytes With diets deficient in potassium but abundant in

(2) J Exper Med. 106 563 574 Oct.1 1957

cellular hyperplasia at the junction of outer and inner zones of the medulla

Epithelial lesions in the nephron proper from glomerulus to collecting tubule were found only in the proximal convolution becoming progressively more frequent in experiments of longer duration and more severe potassium depletion Varying degrees from slight to severe manifestations were present in different nephrons in the same kidney The glomeruli and vessels were normal

Renal tubular lesions in potassium depletion in rats were found only in collecting tubules and proximal convolutions All other portions of the nephron were normal The more severe epithelial lesion in both collecting tubule and proximal convolution began as a swelling of cell bodies increasing to protoplasmic disturbances with disintegration of the mitochondrial pattern followed by rupture of cells and nuclear disappearance and then prolific regenerative hyperplasia In the collecting tubules of the outer zone these epithelial alterations were present in both the clear and the intercalated cells The cellular alterations were associated with inability to concentrate the urine probably as cause and effect

► [Potassium depletion produces a characteristic change of renal function particularly manifested by an inability to concentrate the urine The diagnostic importance of a fixed low specific gravity in hyperaldosteronism is an example of this type of difficulty since most patients with hyperaldosteronism recover their ability to concentrate the urine if they are given enough potassium to repair the deficit The preceding paper indicates that this functional defect is associated with a characteristic anatomic lesion situated in the expected portion of the renal tubule The following abstract outlines some of the other abnormalities associated in clinical practice with potassium depletion —Ed ]

**Clinical Manifestations of Hypopotassemia** are nonspecific and may be found in many severely ill persons with normal levels of serum potassium To determine the frequency of the different signs and symptoms Borys Surawicz Harold A Braun William B Crum Robert L Kemp Seymour Wagner and Samuel Bellet[3] (Philadelphia Gen l Hosp ) studied 50 adults with serum potassium levels under 3 5 mEq /L

*Mortality in patients with hypopotassemia greatly exceeded the total hospital fatality rate* In nearly every case

(3) Am J M S 233 603 616 J 1957

## INBORN ERRORS OF METABOLISM

► ↓ Each of the diseases discussed in the following section appears to be a result of a congenital abnormality in a pecific enzyme or group of en zymes *Although the mechanisms of the inheritance of the e abnormalities* are not always clear it is commonly thought that they reflect the func tional effect of an abnormal or defective gene or group of genes which control the synthesis of the enzyme or enzymes whose absence or faulty function produces metabolic abnormalities —Ed

**Intermediary Purine Metabolism and Metabolic Defects of Gout** are reviewed by James B Wyngaarden[4] (Nat l Inst of Health) Purines are synthesized within the body Sub jects on a diet practically free from purines remain in good health and continue to excrete constant amounts of uric acid The purine ring is synthesized from glycine formyl carbon dioxide glutamine and aspartic acid An early intermediate in the conversion of glycine to the intact purine molecule is glycine amide ribotide

Presumably the formation of uric acid in normal man re sults primarily from degradation of the purine moieties of nucleic acids however glycine may be delivered direct to uric acid without the obligatory intervention of nucleic acids in some persons with gout The free purine bases which re sult from nucleoside cleavage are adenine guanine hypoxan thine and xanthine In mammalian tissue adenine is not de aminated and if it is not reconverted to its nucleoside or nucleotide it may be excreted unchanged in small amounts The other purine bases are readily converted to uric acid by their respective enzyme systems Uric acid is largely ex creted in the urine as such and may be regarded as the end product of purine metabolism in man since the enzyme uri case which oxidizes uric acid to allantoin is not present Normal excretion of uric acid on low purine diets is 300-600 mg daily

The clinical syndrome of gout may well comprise several distinct anomalies of purine metabolism Primary gout the common category is classed as an inborn error of metabo lism Secondary gout accompanying some other disease usually of the hemopoietic system appears to be a conse quence of an acquired acceleration in the degradation of nu cleic acids leading to persistent hyperuricemia

(4) Metabol m 6 244 268 M b 19 7

several factors could have been responsible for the low potassium level and an average of nearly 3 etiologic factors was found in each The patients with the lowest plasma potassium level also had the lowest concentrations of chloride and calcium and were more often alkalotic. Plasma sodium concentration was apparently unrelated Because of anorexia nausea or vomiting 42 patients 84% required parenteral potassium replenishment Degree of anorexia was not related to degree of hypopotassemia

Paralytic ileus was promptly relieved by potassium infusions Intestinal motility increased in 8 patients immediately after intravenous potassium Distention was relieved or bowel sounds became more active after several days of parenteral therapy in 12 Sometimes the effect of intravenous potassium on peristalsis was striking Some patients showed flatulence and 1 had painful abdominal cramps during the infusion None of the patients had respiratory difficulties and the number with normal and abnormal respiratory patterns was evenly distributed After potassium infusion a significant increase in strength occurred in only 4 of the 23 patients in whom it had been decreased Muscle weakness was unrelated to severity of potassium deficiency

Chvostek s sign was present in only 2 patients and muscular twitchings were present in another Serum potassium level was below 2 7 mEq /L in each 2 had hypocalcemia and 1 had alkalosis with normal calcium Numerous patients showed equal degrees of hypocalcemia or alkalosis without Chvostek s sign of twitching Tetany did not occur in any patient during or after potassium administration No consistent change in chlorides or calcium concentration was noted after potassium administration and plasma sodium level decreased oftener than it increased

Clinical findings were of the type often noted in seriously ill patients with or without hypopotassemia Of all clinical abnormalities only decrease of activity of deep tendon reflexes showed some correlation with decrease in plasma potassium level The most significant changes following potassium infusion were improved mental status and increased peristalsis The nonspecific nature of the clinical manifestations of hypopotassemia in these seriously ill mentally beclouded patients emphasizes the importance of laboratory aids in diagnosis of this disorder

out childhood from chilblains Six years before hospitalization he had had rheumatism of small joints accompanying a sore throat and for 2 years there had been skin changes on the fingers He was defi nitely asthenic and complained of episodes of feverish joint swelling and pain Lungs and heart were normal Radial pulse was 80 95 Blood pressure varied from 90/70 to 120/80 A crystalline deposit was noted in the fundus of the left eye Urine was negative for albu min sugar bilirubin and sediment 17 ketosteroid excretion was 12 7 mg /10 ml Urinary output was decreased and there was isos thenuria (dilution 1 010 concentration 1 012) Urine uric acid level was 15 16 mg /100 ml but under treatment (prednisone plus as pirin Atophan® Irgapyrin® alternately later Benemid®) it soon



Fig 12 —Ch on g t of k (C rt y f G tt H A d Kort g G W A b kl p D m t 204 483 499 1957 )

dropped to 0 3 0 9 mg Hemoglobin was 75% red cell count 3 740 000 color index 1 01 leukocyte count 11 000 (later 5 000 9 000) Serum uric acid was originally 16 6 mg /100 ml after treatment 7 10 mg Maximal urea nitrogen content was 68 mg /100 ml Total cholesterol was 186 mg /100 ml (free 67 esterified 119 mg ) Elec trophoresis showed increase of alpha globulin (13%) but no devi ation in total protein (6 6 Gm /100 ml )

X rays showed that bones of both hands and left elbow joint were normal in structure and density and had smooth edges Both capitate bones showed several hazelnut sized roundish cysts of decreased density Wri ts showed signs of arthrosis

Skin e pecially on flexor surfaces of fingers (Fig 122) showed rounded or pointed nodules of match head size They were situated over or near tendons and scattered irregularly either singly or in groups with the overlying skin stretched and thinned showing a sulfur to whitish yellow color shimmering through These nodules when they broke spontaneously exhibited a milky yellow jelly like mass The yellowish color was caused by a mixture of lipids with the uric acid deposit and had led to a diagnosis elsewhere of xanthomatosis

Hyperuricemia may be the sole manifestation of the trait of primary gout usually affecting asymptomatic relatives of patients with gout In primary gout blood urate levels range from 5 9 to 14 mg /100 ml A few patients may occasionally have normal serum levels of urate in the absence of therapy but these are exceptional Considerable uric acid may accumulate in patients with gout even though tophi or x ray evidence of deposits are lacking

The accumulations of urate must result from derangements in the normal balance between rates of urate formation and of excretion and destruction There is no clearcut explanation but most of the evidence indicates that in a significant proportion of patients with primary gout excessive amounts of urates are produced directly rather than from nucleotides accounting for the hyperuricemia and associated increase in basal urate excretion Older treatises ascribed the disturbances of uric acid metabolism to a renal defect in urate excretion However young patients with gout have normal urate clearances and often excrete increased amounts of urate The low urate excretion commonly found in late gout is probably due to the renal damage which is a common complication

The incidence of overt gout is low in polycythemia myeloid metaplasia chronic leukemia and other hemopoietic disorders but when present represents not an inborn error of metabolism but an acquired exaggeration of the catabolism of nucleic acids with resultant flooding of the body with the products of such breakdown including both intermediary purines and the metabolic end product uric acid

Uric acid per se is not the cause of acute gouty arthritis Acute gout cannot be produced in normal or gouty persons by administering uric acid orally intravenously or even subcutaneously around the joints Further in treating acute gout there is no correlation between the uricosuric effect of a drug and clinical response Factors precipitating the acute gouty attack remain unknown

► [For the technically minded further information may be obtained from another article by Wyngaarden (J Clin Invest 36 1508 1957 —Ed ]

**Chronic Gout of Skin** H A Gottron and G W Korting[5] (Univ of Tubingen) report an interesting case

Butcher 22 had no history of gout arthropathy or metabolic disease in his family He had a severe fall at age 6 and suffered through

(5) A h kl p D m t 204 483 499 1957

year 2 similar attacks Serologic test for syphilis was po itive and porphobilinogen was present A menstrual period began 3-4 days after each attack

She was given two 50 mg injections of progesterone 48 hours apart A menstrual period ensued 4 days later associated with an epi sode similar to the preceding ones During the next 2 years she had 8 attacks 3 of which followed progesterone induced menstrual flow 4 of which preceded spontaneous menstrual periods and only 1 of which occurred during a period of amenorrhea On one other occasion pro gesterone was given causing a menstrual period but without an at tack of porphyria

Piperazine estrone sulfate 9 mg daily for 4 weeks was followed by an anovulatory period without complication Several weeks later the patient spotted spontaneously and had an acute attack of por phyria which required hospitalization She subsequently had two spontaneous periods which were pain free and anovulatory For the next 6 months she was given 2 cc injections of a long acting estro gen at monthly intervals responding to each with withdrawal bleed ing Dark urine accompanied only one period but no pain was noted

This case is particularly interesting because of the fre quency with which an acute attack of porphyria could be precipitated with endogenous or exogenous progesterone

**Treatment of Acute Porphyria with Chelating Agents Report of 21 Cases** is made by Henry A Peters Sherwyn Woods Peter L Eichman and Hans H Reese (Univ of Wisconsin) Acute hepatic porphyria inherited as a men delian dominant is characterized by recurrent gastrointes tinal psychiatric and neurologic symptoms singly or com bined The mortality rate when associated with severe neuropsychiatric manifestations is cited as 80 90%

The 21 patients had porphobilinogenuria and 19 excreted uroporphyrins Clinical syndromes were varied Eight had bulbar symptoms of dysphagia diplopia anisocoria and fa cial and/or laryngeal palsies 5 had jacksonian seizures and 7 grand mal seizures 13 had psychiatric symptoms 8 showed peripheral neuropathy and 12 complained of obstipation Severe pain was frequent Eleven patients were treated with BAL A 10% solution in 20% benzyl benzoate in peanut oil 50 1 200 mg /24 hours in divided doses was given for 4 60 consecutive days several received 100 300 mg weekly for as long as 2 years In 6 patients BAL was combined with intravenous EDTA 1 10 Gm /24 hours diluted in 5% glu cose in water in a ratio of 2 5 5 Gm EDTA/1 000 cc ad ministered over 2 4 hours for 2 5 consecutive days

(7) An I t M d 47 889 899 N mb 19 7

Along with these skin changes the patient displayed signs of chronic arthropathy finger joints especially the metacarpal and middle interphalangeal were *definitely swollen and inflamed in the acute painful stage End joints showed supracapsular hyperostotic thickening* and extensor tendons showed rice sized nodules of firm to hard consistency corresponding to those on flexor tendons The olecranian bursa was edematous and there was a hard nodule on the elbow The suprapatellar bursa was also swollen

Smears prepared from contents of the nodules showed numerou lancet like colorless crystals *often in clusters resembling needles of fatty acid these dissolved on heating and on cooling formed needles* in yellowish white bundles Other slides showed large amounts of morphologically undifferentiated salts with a negative murexide reaction along with brown amorphous clumped masses of regularly formed needles irregular plaques cholesterol slabs also regularly formed brownish crystals These salts were partly dissolved by warm*ing and partly after addition of 10% hydrochloric acid and remained partly undissolved Urate crystals were seen in slides treated with HCl*

Histologically beneath a hyperkeratotic epidermis in the middle and deep layers of the cutis there were areas of infiltration of lymphocytes and giant cells of foreign body type Reaction for mono o dium urate was positive

Noteworthy features of this case aside from the rare skin lesions were the crystalline deposit in the eyegrounds increase of $alpha_2$ globulin high blood uric acid of 16 6 mg/100 ml (highest recorded is 19 mg) and functional kidney deficiency shown by the concentration dilution test

**Progesterone Induced Porphyria Case Report** is presented by Edithe J Levit John H Nodine and William H Perloff[6] (Gen l Hosp Philadelphia) Acute porphyria occurs two to three times more frequently in women than in men and is first manifest during the 2d to 5th decades It is characterized by intermittent excretion of large quantities of uroporphyrin and coproporphyrin so that the urine is dark brown or port wine colored acute colicky lower abdominal pain and various neurologic manifestations are usually present The initial attack may be noted at the menarche or at a subsequent menstrual period It may be associated with amenorrhea or menstrual irregularities and a tendency toward exacerbation at the time of menses has been reported These relations suggest an endocrine factor as a causal or precipitating agent in some women

Woman 27 first noted menstrual irregularities 4 years earlier after 3 years she had the first episode of acute porphyria and next

(6) Am J Med 22 831 33 May ----

year 2 similar attacks Serologic test for syphilis was positive and porphobilinogen was present A menstrual period began 3-4 days after each attack

She was given two 50 mg injections of progesterone 48 hours apart A menstrual period ensued 4 days later associated with an episode similar to the preceding ones During the next 2 years she had 8 attacks 3 of which followed progesterone induced menstrual flow 4 of which preceded spontaneous menstrual periods and only 1 of which occurred during a period of amenorrhea On one other occasion progesterone was given causing a menstrual period but without an attack of porphyria

Piperazine estrone sulfate 9 mg daily for 4 weeks was followed by an anovulatory period without complication Several weeks later the patient spotted spontaneously and had an acute attack of porphyria which required hospitalization She subsequently had two spontaneous periods which were pain free and anovulatory For the next 6 months she was given 2 cc injections of a long acting estrogen at monthly intervals responding to each with withdrawal bleeding Dark urine accompanied only one period but no pain was noted

This case is particularly interesting because of the frequency with which an acute attack of porphyria could be precipitated with endogenous or exogenous progesterone

**Treatment of Acute Porphyria with Chelating Agents Report of 21 Cases** is made by Henry A Peters Sherwyn Woods Peter L Eichman and Hans H Reese[7] (Univ of Wisconsin) Acute hepatic porphyria inherited as a mendelian dominant is characterized by recurrent gastrointestinal psychiatric and neurologic symptoms singly or combined The mortality rate when associated with severe neuropsychiatric manifestations is cited as 80 90%

The 21 patients had porphobilinogenuria and 19 excreted uroporphyrins Clinical syndromes were varied Eight had bulbar symptoms of dysphagia diplopia anisocoria and facial and/or laryngeal palsies 3 had jacksonian seizures and 7 grand mal seizures 13 had psychiatric symptoms 8 showed peripheral neuropathy and 12 complained of obstipation Severe pain was frequent Eleven patients were treated with BAL A 10% solution in 20% benzyl benzoate in peanut oil 50 1 200 mg /24 hours in divided doses was given for 4-60 consecutive days several received 100 300 mg weekly for as long as 2 years In 6 patients BAL was combined with intravenous EDTA 1 10 Gm /24 hours diluted in 5% glucose in water in a ratio of 2 5 5 Gm EDTA/1 000 cc administered over 2-4 hours for 2 5 consecutive days

(7) An I t Med 47 889 899 N mbe 19

After the diagnosis had been made or suspected barbiturates sulfonamides alcohol heavy metals, exposure to oil paints solvents and sunbathing were studiously avoided Thorazine® Demerol® paraldehyde Frenquel® and intravenous procaine were occasionally used Exceptional nursing care tracheotomy and careful attention to fluid and electrolyte balance were essential in each case

Of the 20 patients with acute intermittent disease 13 improved as did the patient with mixed porphyria Four patients responded equivocally 2 showed no change and 1 died despite steroid therapy and BAL No difference was discernible in response to BAL and EDTA although the response to BAL seemed more rapid

Although control studies were not included spontaneous remissions are unpredictable and variation in severity characterizes this disease the results suggest in view of the high mortality reported in severe cases by others that the prompt improvement in these severely ill patients is attributable to therapy with chelation

► [This form of treatment appears to be helpful in many cases Tranquilizers which have also been recommended for treatment of this condition (1957 58 Year Book p 720) have been less successful in my limited experience Readers interested in porphyria will find Waldenstrom's review (Am J Med 22 758 1957) of value —Ed ]

**Roentgenographic Abnormalities of Skeletal System in Wilson s Disease (Hepatolenticular Degeneration)** in 20 patients are described by *Nathaniel Finby* and *A G Bearn*[8] (Cornell Med Center) Absorption of copper from the intestinal tract is increa ed in Wilson s disease and probably copper deposited in the brain and liver is responsible for the clinical syndrome Clinical manifestations usually appear in young persons aged 12 20 Symptoms include tremor rigidity dysarthria and dysphagia due to disorganization of the lenticular region of the brain and cirrhosis of the liver Kayser Fleischer ring Urinary copper is increased although serum copper is low Normally most copper is bound to the serum globulin ceruloplasmin but in these patients more is bound to albumin because the serum ceruloplasmin is decreased more than is serum copper Many patients show increased amino acid excretion particularly threonine and cystine and phosphaturia due to decreased tubular reabsorption of phosphate

(8) Am. J Roentgen l 79 603 611 Ap l 1958

The 20 patients had systematic roentgenographic skeletal survey and only 6 showed normal osseous structures Seven patients had osteomalacia varying from severe bone demineralization to patchy rarefaction 2 had Milkman s pseudo fractures and 9 had unusual bone fragmentation at joint margins (Fig 123) Cartilage injury was noted in 11 patients



Fig 123 —O seo a le w man, 37 with Wilson d sease I 23 y d ra on Hand d w t how seve osteoarthrit and bon f agmentat on m t mark d w t Met porb la g al jo t sh w bchondr l bon g la ty (Co rt y f F aby N d Hearn A G Am J Roentgen l 79 603 611 Ap l 1958)

in whom severe osteoarthritis was present 8 of these were under age 40 Patients with Wilson s disease tend to have fractures which may be associated with increased bone fragility due to disturbed phosphorus metabolism but possibly may in part be related to the abnormal copper metabolism Certain a pects of Wilson s disease are remarkably similar to those of the Fanconi syndrome

**Renal Function in Wilson s Disease** Hepatolenticular degeneration (Wilson s disease) is a hereditary disorder char

acterized by a variety of metabolic defects excessive absorption of copper from the intestinal tract increased total copper content of the body abnormally low ceruloplasmin (the main copper carrying protein of serum) and excessive urinary excretion of copper Aminoaciduria occurs in many cases and uricosuria and glycosuria are found in some A G Bearn T F Yu and A B Gutman[9] (New York) studied 9 patients by simultaneous clearance technics

The glomerular filtration rate was reduced in 8 patients and albumin excretion was increased in 4 Blood urea nitrogen was not elevated in any patient Renal plasma flow was consistently reduced and the filtration fraction $C_{I}$ [illegible] $/C_{PAH}$ was higher than normal in most Tubular excretory capacity was reduced in the 6 patients in whom it was measured Tubular reabsorptive mechanism for alpha amino nitrogen urate inorganic phosphate and glucose were impaired Plasma urate levels were below the minimum normal level and urate clearance was strikingly increased Phosphate clearance was also increased

Probenecid is a potent inhibitor of renal tubular excretory systems markedly suppressing tubular transport of para aminohippurate (PAH) Such a response was induced in patients with Wilson s disease but was somewhat less than that seen in a normal subject and about equal to that in patients with gout who had intact kidney function Urate clearance increased about 75% in contrast to a 300% increase in patients with gout

These studies corroborate the substantial reduction in renal plasma flow and decreased glomerular filtration rate reported by others The degree of impairment roughly paralleled the severity or duration of overt disease suggesting progressive deterioration of the renal vascular bed

Excessive aminoaciduria in Wilson s disease has been attributed to inadequate tubular reabsorption The high clearance of alpha amino nitrogen even though plasma levels were normal confirms this hypothesis Similarly diminished tubular reabsorption of filtered urate explains the uricosuria and low plasma urate levels as confirmed by the augmented urate clearance ratio consistently found In all 4 cases studied maximum tubular capacity to reabsorb glucose was reduced even though spontaneous glycosuria was not

(9) J Cl n I t 36 110 1114 J ly 195

usually present Failure to find increased excretion of glucose does not preclude a considerable defect in the capacity to transport glucose across the tubular epithelium

These studies indicate progressive deterioration of certain discrete tubular functions glomerular filtration and renal plasma flow with advance of the disease These renal changes may reasonably be ascribed to the deleterious effects of accumulation of copper in the kidneys The renal abnormalities thus may be secondary to a disturbance in copper metabolism rather than a direct consequence of the effect of the abnormal gene on renal function

► [Bearn and McKusick (J A M A 166 904 Feb 22 1958) have also described a peculiar bluish pigmentation of the lunulae of the fingernails in 2 patients with Wilson s disease —Ed ]

► ↓ The aminoaciduria of Wilson s disease is only one of several types of excessive amino acid excretion in the urine The similarity of hepatolenticular degeneration to the Fanconi syndrome has already been mentioned The next 2 papers describe two probably unrelated diseases in which the amino aciduria does not produce systemic effects (as it does in Wilson s disease or in the Fanconi syndrome) but does produce renal difficulties with stone formation —Ed

**Renal Clearance of Lysine in Cystinuria Pathogenesis and Management of This Abnormality** The urine in cystinuria contains excessive amounts of three other amino acids—lysine arginine and ornithine Larger amounts are excreted in the homozygous than in the heterozygous form Apparently the defect is not a generalized disturbance of amino acid metabolism but impaired renal tubular reabsorption of particular amino acids P D Doolan H A Harper M F Hutchin and E L Alpen[1] (US Naval Hosp Oakland Calif ) report studies in 4 patients with cystinuria

The average fasting plasma lysine concentration was 2 4 mg /100 ml compared with the normal of 3 2 mg /100 ml This suggests that the plasma concentration of lysine is lower than normal Previous studies demonstrated a reduction in the plasma concentration of cystine The glomerular filtration rate was normal in 2 patients slightly reduced in 1 and definitely reduced in 1 Cystinuria per se has no effect on renal hemodynamics but any changes which occur are secondary to the complications of calculi and infection

In normal subjects the endogenous clearance of lysine is less than 1 ml /minute and tubular reabsorption is virtually complete in the fasting state In patients with cystinuria the endogenous clearance approximates 55 ml /minute and

(1) Am J M d 23 416 425 S pt mbe 1957

reabsorption is about 45% Though the actual concentrations measured are low significant reabsorption of lysine does occur

Tubular reabsorption of alanine glutamine glycine histidine isoleucine leucine methionine phenylalanine proline serine threonine tryptophan tyrosine and valine was normal fasting and after loading When the lysine plasma concentration was increased no significant quantity of the added amount filtered was reabsorbed and the clearance of lysine approached that of inulin Both normal subjects and patients with cystinuria showed an increase in glycocyamine excretion after administration of equimolar amounts of arginine and glycine

An important factor in renal calculi which develop in cystinuria is the insolubility of cystine Treatment should be directed toward decreasing cystine excretion or rendering it less likely to precipitate Therapy directed toward the tubular reabsorption mechanism holds little chance of success since the transport system appears to be congenitally absent However by decreasing dietary intake the plasma level will be decreased and cystine excretion reduced Since urinary cystine is derived primarily from methionine supplementing a diet low in methionine with a methyl donor such as betaine might further decrease cystine excretion by decreasing conversion of methionine to homocystine By round the clock alkalinization and maintenance of a dilute urine opportunity for cystine precipitation is minimized The possibility of infection particularly with urea splitting organisms must be considered

A suggested explanation for the tubular defect in cystinuria is that in the homozygous form the transport system is present in only trace amounts In the fasting state a minute amount of lysine can be reabsorbed but the tubules are unable to reabsorb any further amount and on loading with lysine the clearance value approaches that of inulin The transport system may be of the membrane carrier type Any reabsorption which does occur is accomplished by an active mechanism Passive diffusion is insignificant

**Glycinuria Hereditary Disorder Associated with Nephrolithiasis** Cystine was discovered in a bladder stone 150 years ago and since then excessive amino acid excretion in the urine has been studied extensively Lately this has been

aided by paper chromatographic methods Andre de Vries Shaul Kochwa Jacob Lazebnik Menahem Frank and Meir Djaldetti[2] (Petah Tikva Israel) report a new aminoaciduria glycinuria which was detected by chromatography of the urine from a patient with recurrent bilateral nephrolithiasis Excessive glycine excretion was found in 3 other members of the family and 2 of these also had nephrolithiasis

Woman 20 had recurrent renal colic since age 2 and renal calculi were demonstrated at age 6 She had had pyelotomy nephrostomy and nephrectomy on the left but subsequently began having the same difficulty on the right Renal function serum electrolytes calcium phosphorus and alkaline phosphatase were normal The amino acid pattern of the urine showed a prominent spot at the location of glycine but was otherwise normal A rough estimation indicated 24 hour excretion to be about 650 mg and on 6 consecutive days excretion ranged from 800 to 1 200 mg compared to the normal of 156 mg /24 hours Serum glycine levels were normal After an intravenous glycine load glycine excretion was excessive Analysis of the renal calculus showed it contained 0 5% glycine

Chromatographic examination of the urine of members of the patient s family showed excessive glycine excretion with otherwise normal amino acid patterns in the sister mother and maternal grandmother The father maternal uncle and a daughter aged 2 had normal glycine excretion The sister had a history of renal colic and a stone was demonstrated The grandmother had had renal colic but no stones could be found

It appears from the pedigree that the glycinuria is a dominant sex limited character though the pedigree is too small for certainty The glycinuria was due to a renal mechanism Failure to reabsorb glycine was not associated with defective reabsorption of other amino acids or of phosphate or glucose

Increased glycine excretion due to renal disturbance is a common feature of syndromes in which there is gross aminoaciduria with abnormal amino acid excretion patterns such as the de Toni Fanconi syndrome Wilson s disease and H syndrome In some of these glycine excretion is only moderately increased in others it is the most striking abnormality Only a few renal aminoacidurias have been described in which excessive glycine excretion was the main abnormality In the family described here glycinuria was the only abnormality and was associated with nephrolithiasis

**Aminoaciduria and Hypermetabolism in Progeria** A Harell Steinberg A Szeinberg and B E Cohen[3] (Tel Hasho

(2) Am J M d 23 408 415 S p mbe 1957
(3) A b D Ch ldhood 32 401 403 O t be 1957

mer Government Hosp Israel) report the following case

Boy 5½ had typical clinical findings of progeria Laboratory studies revealed hypoaminoacidemia hyperaminoaciduria increased $I^{131}$ thyroid uptake and high protein bound iodine values in the blood Treatment with propylthiouracil and methyltestosterone 50 mg daily each effected a weight gain of 3 4 kg in 2 months and a height increase of 4 cm The patient s appearance was otherwise unchanged and the treatment had no effect on the aminoaciduria An attempt to influence the alopecia with cortisone and ACTH failed

Aminoaciduria can be caused by overflow (an increase in blood amino acid level as a result of liver necrosis extensive muscular atrophies hyperthyroidism etc ) or by widespread renal damage or it may be primary as in the de Toni Fanconi syndrome hepatolenticular degeneration or cystinuria The constant finding in the present case of aminoaciduria accompanied by a low blood amino acid level seems to indicate a defect similar to that of the de Toni Fanconi type

The thyroid gland appears to play no part in the pathogenesis of hypermetabolism in progeria However in the present case the rapid and increased absorption of radioactive iodine suggests that the thyroid was overactive causing the increased metabolism

**A Disease Probably Hereditary Characterized by Severe Mental Deficiency and Constant Gross Abnormality of Amino Acid Metabolism** Several congenital disorders are now known to be due to comparatively simple biochemical abnormalities phenylketonuria galactosemia Wilson s disease the so called organic aciduria syndrome H disease and goitrous cretinism All are hereditary J D Allan D C Cusworth C E Dent and V K Wilson[4] describe a *family in* which 2 of 4 children of unrelated parents showed severe mental retardation

Both affected sibs had grossly abnormal EEG s One had several epileptiform convulsions followed by ataxia lasting a few days Both had friable hair and systolic murmurs but were otherwise healthy and normal on physical examination

Both had an identical and highly specific gross disorder of mino acid metabolism not present in any other member f the family *They constantly excreted into the urine large* uantities of a new and unidentified substance with only minor changes in pattern of the amino acids excreted The

(4) La t 1 182 187 J n 25 1958

abnormal substance was found in low concentration in the plasma of the children but was present in much higher concentration in their cerebrospinal fluid

The clinical aspects of this form of mental deficiency are not characteristic During the first year of life development appeared normal The excessive friability of the hair was unusual Chromatographic analysis of the urine revealed excretion of a grossly abnormal amino acid one ninhydrin reacting substance and a small amount of another substance close to it on the chromatogram Neither of these match in chromatographic behavior any of the known amino acids The amino acids normally excreted—glycine alanine and taurine—are excreted in these urines in smaller quantities than usual A deliberate search for the condition among 1 500 mentally defectives has so far failed to reveal another case

The presence of low concentrations in the plasma of the affected children and higher concentrations in the cerebrospinal fluid suggests that the substance may be formed in the brain or some other organ close to the cerebrospinal fluid from which it passes into the plasma and is rapidly excreted by the kidneys

**One Year Controlled Study of Effect of Low Phenylalanine Diet on Phenylketonuria** The biochemical lesion responsible for the disease is a deficiency of the hepatic enzyme phenylalanine hydroxylase which normally converts phenylalanine to tyrosine The principal clinical features include severe mental retardation blonde hair blue eyes certain neurologic findings such as hyperreflexia agitated behavior and finger posturing minor choreoathetosis and occasionally true spastic paraplegia Eczema or other skin conditions and epileptic seizures occur in one third of the patients and 80% have EEG abnormalities

A diet deficient in phenylalanine has been reported beneficial but the few patients treated and the variable manifestations make evaluation difficult David Y Y Hsia W Eugene Knox Karl V Quinn and Richmond S Paine[5] (Harvard Med School) studied 24 patients with phenylketonuria They were divided into 12 matched pairs comparable as to age sex intelligence and length of institutional placement One member of each pair was selected to receive

(5) Pediat ic 21 178 0 F bru ry 1958

a phenylalanine deficient diet for 12 months The other received a control diet identical in appearance and flavor

After 12 15 months the patients were evaluated as to adequacy of chemical control and changes observed in intelligence behavior skin condition hair color seizures and EEG abnormalities Many difficulties were encountered in maintaining the patients on these diets Several developed malnutrition severe enough to require discontinuance of the diet temporarily The low phenylalanine diet is undoubtedly dangerous unless the patient is observed closely

The plasma concentration of phenylalanine is the only reliable guide in evaluating therapy It may remain high when the urine phenylpyruvate is negative If it becomes extremely low *intake of phenylalanine may have to be increased* slightly Death in status epilepticus has been reported possibly associated with extremely rapid decrease in plasma phenylalanine to nearly zero

Possible beneficial effect on intelligence was limited to 4 patients aged 6 months 7 months 1½ years and 3 years at the time the diet was begun Improvement in skin condition behavior and possibly EEG s was noted in the older patients but such benefits would not seem to justify the difficulties and dangers of dietary therapy

The metabolic disturbances associated with elevated concentration of phenylalanine in the plasma characteristic of phenylketonuria interfere with normal cerebral development rather than with the function of a normally developed brain Recognition at the earliest possible age and prompt institution of dietary control are essential if the therapeutic benefits of a low phenylalanine diet are to be conclusively evaluated

► [Additional more optimistic information is presented by Woolf *et al* (Arch Dis Childhood 33 31 1958) who studied 10 patients with phenylketonuria treated by a low phenylalanine diet and feel that most patients with this disease can benefit from dietary control Hsia s study *is well controlled and certainly seems justified in raising a question as to the long term advantages of the diet with restricted phenylalanine* Clearly more work needs to be done —Ed ]

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